PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/74 — A1

(11) International Publication Number: WO 91/18613

(43) International Publication Date: 12 December 1991 (12.12.91)

(21) International Application Number: PCT/US91/03864

(22) International Filing Date: 31 May 1991 (31.05.91)

(30) Priority data:
531,847 1 June 1990 (01.06.90) US

(60) Parent Application or Grant
(63) Related by Continuation
US 531,847 (CIP)
Filed on 1 June 1990 (01.06.90)

(71) Applicant *(for all designated States except US)*: RESEARCH CORPORATION TECHNOLOGIES, INC. [US/US]; 6840 East Broadway Boulevard, Tucson, AZ 85710 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : SHIVELY, Merrick, L. [US/US]; 549 Adams Avenue, Louisville, CO 80027 (US).

(74) Agents: SULLIVAN, Sally, A. et al.; Greenlee and Associates, 5370 Manhattan Circle, Suite 201, Boulder, CO 80303 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: SELF-EMULSIFYING GLASSES

(57) Abstract

The present invention provides compositions and method for the preparation of emulsions and multiple emulsions. Specifically, the invention provides solids which are self-emulsifying glasses which, on contact with a sufficient amount of an aqueous phase, form emulsions or multiple emulsions without input of emulsive mixing. Emulsions and multiple emulsions produced from the self-emulsifying glasses are encompassed by this invention. The self-emulsifying glasses are prepared from certain matrix compounds and an oleaginous material by a solvent method. The glass results from removal of solvent from a combination of matrix compound, oleaginous material and a solvent which dissolves substantially all of the matrix compound. Multiple emulsions result from glasses in which the oleaginous phase is a primary, e.g. water-in-oil emulsion. The glasses and emulsions produced therefrom are particularly useful pharmaceutical, food and cosmetic applications.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CS	Czechoslovakia
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GN	Guinea
GR	Greece
HU	Hungary
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
PL	Poland
RO	Romania
SD	Sudan
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America

SELF-EMULSIFYING GLASSES

Cross-reference to Related Applications

This application is a continuation-in-part of U.S. patent application serial number 07/531,847, filed June 1, 1990, which is incorporated, in its entirety, by reference herein.

Field of the Invention

This invention is in the field of emulsion technology and relates more specifically to compositions and methods for the preparation of emulsions and multiple emulsion and applications of such compositions and emulsions in the pharmaceutical, food or cosmetic fields.

Background of the Invention

A number of pharmaceuticals are abandoned every year in the pharmaceutical industry not because the compounds are found to be inactive, but rather because they cannot be solubilized in an FDA approved solvent for delivery to the patient. This problem is quite common for chemotherapeutic agents, which can have extremely low or no water solubility due to their nonpolar nature. Additionally, compounds useful in the cosmetic, food, liquor, photographic, chemical or biomedical industries, may currently not be utilized for lack of an effective method to keep them solubilized or suspended. A method and vehicle that can solubilize or suspend such nonpolar compounds have numerous pharmaceutical and industrial applications.

In general, the method for preparation of a vehicle for solubilizing nonpolar material should preferably be simple, i.e., should not involve numerous process steps or special skills to manufacture. It is also preferred that the method be economical, e.g., not involve a great deal of energy input.

The vehicle should preferably be capable of lengthy storage without compromising its effectiveness as a delivery agent. To reduce transportation and storage costs, the vehicle should be capable of being stored in a compact form. For example, if the vehicle can be stored as

a dry solid, this can reduce the vehicle's weight and volume, which in turn can reduce transportation and storage costs.

If such a vehicle is to have use for pharmaceuticals, foods or other comestibles, it should not contain toxic materials. Additionally, such vehicles preferably do not impart an unpleasant or disagreeable flavor to edible products incorporated in them. Vehicles for topical applications, in pharmaceutical or cosmetic applications, should be non-toxic and non-irritating. Many surfactants are toxic, can cause irritation or can impart undesirable flavors; thus, they have limited use for pharmaceuticals or edible products.

An ideal vehicle should be stable at a variety of pHs and temperatures to ensure its widest application.

For certain pharmaceutical applications, the vehicle should preferably be capable of leaving the vascular system to enter intercellular fluids so as to deliver the pharmaceutical to cells. To pass through intercellular junctions in vascular endothelium, the vehicle size should be less than about 200 Å (0.2 μm).

Existing methods and vehicles to solubilize lipophilic compounds can involve complex methods of manufacture, requiring highly skilled labor, or can require the input of

a considerable amount of energy. Existing methods and vehicles can also involve components that are toxic or are sensitive to variations in pH and temperature. Such methods and vehicles, particularly those applied to pharmaceutical use, include surfactant-containing emulsions and multiple emulsions, liposomes, glass dispersions and coprecipitates.

Emulsions in the prior art, while capable of solubilizing or suspending hydrophobic compounds in an aqueous environment, can be expensive to manufacture, can be unstable and usually contain toxic surfactants. The expense of manufacture is due largely to the use of energy-consuming devices that impart sufficient shear force to mix the phases and produce the appropriate particle size (A. Weiner (1990) BioPharm 2:16-21). Shear stress devices, such as colloid mills, rotary-blade mixers, valve-type homogenizers, the Microfluidizer, French press pressure systems, ultrasonic baths or sprayers, and membrane based extruders, require considerable energy to produce the desired particle size. The operation of these devices requires the additional expense of skilled labor (P. Walstra (1983) Encyclopedia of Emulsions: Basic Theory, Vol. 1:120 (P. Becher ed.)). Further, high shear devices, particularly those in which the temperature is unregulated, can inactivate compounds carried in the internal phase (A. Sadana (1989) BioPharm 2:14-25; and A. Sadana (1989) BioPharm 2:20-23).

Multiple emulsion systems have recently been described for use in a variety of pharmaceutical and industrial applications (Davis, S.S. and Walker, J.M. (1987) Meth. Enzy. 149:51-64; Davis, S.S. (1981) Chemistry and Industry 3(October):683-687). Water-in-oil-in-water emulsions, for example, can be employed to carry, transport or protect water-soluble compounds in their internal aqueous phase. The internal oil phase of such multiple emulsions can solubilize lipid-soluble compounds. Multiple emulsions can be generated when an emulsion inverts from one type to another or by re-emulsification of a primary emulsion (Florence, A.T. and Whitehill, D. (1982) Int'l. J. Pharmaceutics 11:277-308; Matsumoto (1983) J. Colloid Interface Sci. 94:362-368; Frenkel et al. (1983) J. Colloid Interface Sci. 94:174-178). The existing methods most often used for applications to pharmaceuticals is re-emulsification which employs at least two different surfactants (one having high HLB, one having low HLB). It is reported that, however, that practical applications of multiple emulsions have been limited due to their inherent instability (Omotosho, J.A. et al. (1988) J. Microencapsulation 6:183-192; Magdassi, S. et al. (1984) J. Colloid and Interface Sci. 97:374-379). Multiple emulsions containing lower levels of surfactants and which are significantly more stable will greatly extend the useful applications of such vehicles.

Related systems, gelatin sphere-in-oil-in-water multiple emulsions, have been described in relation to their potential use in drug delivery (Yoshioka et al. (1982) Chem. Pharm. Bull. 30:1406-1415). In these systems the internal water droplets are replaced with gelled gelatin microspheres. In these multiple emulsions the S/O emulsion was formed by ultrasonication of an oil phase containing surfactants and an aqueous gelatin solution (20%). The S/O/W emulsion was generated by dispersing the S/O emulsion into another aqueous gelatin (1%) solution. Lyophilization of the S/O/W emulsion resulted in "bulky piles of oil droplets" which on situation gave the original S/O/W emulsion.

Improved stability of multiple W/O/W emulsions is reported to result when polymerizable non-ionic surfactants which form interfacial membranes are employed (Law et al. (1984) J. Pharm. Pharmacol. 36:50; Law et al. (1984) Int'l. J. Pharma. 21:277-287). Addition of macromolecules such as albumin to W/O/W compositions are reported to result in the formation of interfacial films which stabilize multiple emulsions. These improved systems still require the use of multiple emulsifying agents.

In emulsion manufacturing, the energy input necessary to produce the desired particle size can be reduced by using combinations of emulsifying agents that closely match the hydrophile-lipophile balance (HLB) requirement of the lipid

phase (A. Weiner (1990) BioPharm 2:16-17). Unfortunately, most of these agents are irritating and have limited in vivo use (Swarbrick, J. (1965) J. Pharm. Sci. 54:1229). The necessity of concentrated irritating emulsifiers can severely limit the use of emulsifier-containing preparations in pharmaceutical applications.

Emulsifier-containing emulsions also can exhibit instability to changes in pH and temperature, resulting in coalescence of the emulsion particles and ultimately in phase separation (J. Collett & L. Koo (1975) J. Pharm. Sci. 64:1253; and P. Elworthy & F. Lipscomb (1968) J. Pharm. Pharmacol. 20:817).

Liposomes are a thermodynamically stable dispersal system (H. Hauser (1984) Biochem. Biophys. Acta 772:37) capable of solubilizing compounds (A. Janoff et al. (1985) Euro. Patent Publ. No. 185680). Liposomes can, however, be unstable under certain conditions (L. Guo et al. (1980) Lipid Res. 21:993; C. Alving & R. Richards (1983) The Liposomes (M. Ostro ed.; D. Papahadjopoulas (1962) Proc. Soc. Exper. Biol. 111:412). Liposomes may be antigenic/immunogenic (C.Alving (1986) Chem. Phys. Lipids 40:303) and can be too large (at least 600 Å in diameter) to allow their transport through intercellular junctions in the vascular endothelium (N. Simionesu et al. (1975) J. Cell Biol. 64:586; G. Gregoriadis (1979) Drug Carriers in Biology and Medicine, pp. 287-341). Moreover, the

manufacture of liposomes is expensive in that it requires special skills and equipment and can be energy intensive (F. Defrise-Quertain et al. (1984) Liposome Technology, Vol. 2, pp. 1-17; and F. Szoka & D. Papahadjopoulis (1980) Ann. Rev. Biophys. Bioeng. 9:467; A. Weiner (1990) Biopharm 2:17-18; Ostro (1988) Liposomes as Drug Carriers, p.855 (G. Gregoriadis, ed.)).

Glass dispersions are solids formed by incorporating a medicinal within a melt, thus forming a glass dispersion upon solidification. Such materials are used in tablets, capsules or other dosage units to increase dissolution, absorption, and therapeutic efficacy of medicinals. The glass solid dispersion is formed by the melting or fusion of a carrier and a drug followed by rapid cooling. The carrier is soluble in a solvent; mixing with the solvent results in the rapid dissolution of the carrier and the molecular dispersion of the drug in the matrix of the carrier. One disadvantage of this method is that either the drugs or carriers can decompose, evaporate or be oxidized during the fusion process (W. Chiou & S. Riegelman (1971) J. Pharm. Sci. 60:1283). A further disadvantage is the manufacturing expense incurred by the input of heat energy. Finally, the drug must be soluble or miscible in the fused carrier compound in order to form a glass dispersion solid. For example, in J. Kanig (1964) J. Pharm. Sci. 53:188-192, the investigator was unable to disperse or dissolve castor oil in molten mannitol.

References that describe glass solutions using saccharides as carrier compounds include L. Allen et al. (1977) J. Pharm. Sci. 66:494-496; W. Chiou & S. Riegelman (1971) J. Pharm. Sci. 60:1281-1302; and J. Kanig (1964), supra.

Coprecipitate solids can be mixed with a solvent to form a solution. Coprecipitate solids are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent (W.Chiou & S.Riegelman (1971) J. Pharm. Sci. 60:1283). Coprecipitates have been produced with various polymers. References describing such coprecipitates include W. Chiou & S. Riegelman (1971) J. Pharm. Sci. 60:1376-80; E. Stupak & E. Bates (1972) J. Pharm. Sci. 61:400-403; W. Chiou & S. Riegelman (1971) J. Pharm. Sci. 60:1281-1302; A. Simonelli et al. (1969) J. Pharm. Sci. 58:538-549; and T. Tachibana & A. Nakamura (1965) Kolloid-Zeitschrift und Zeitschrift für Polymere 203(2):130-133. However, none of these references report coprecipitates containing an oil or lipid component. A disadvantage associated with existing coprecipitate methods is that a common solvent must be found for both the drug and the carrier. This necessarily restricts the possible combinations of drug and carrier to those that have a common and non-toxic solvent.

The novel method of this invention supplies emulsion systems and multiple emulsion systems that obviate many problems inherent in the foregoing methods and systems. The method provides a novel glass that, on addition of a selected liquid aqueous phase, forms an emulsion that contains no toxic surfactants (or in the case of multiple emulsions requires only one surfactant). The method of producing the glass is simple. The equipment used in this method for production of the glass and generation of an emulsion from the glass requires far less energy than that required for production of liposomes and surfactant-containing emulsions. An emulsion can be generated from the glass of this invention by simply contacting it with a suitable aqueous phase (e.g., water); no work is necessary to form the emulsion. The resulting emulsion is stable under a variety of pH and temperature conditions. The emulsion can be formulated to have particles less than about 0.2 μm in diameter to allow transport through vascular endothelial intercellular junctions. In contrast to prior art methods, multiple emulsions can be generated from a solid material, a glass, having an extended shelf-life simply by addition of a selected aqueous phase. In contrast to existing coprecipitation systems, the emulsions of the subject invention contain an oil phase that can optionally be used to solubilize hydrophobic active ingredients. Further, the inclusion of an oil component in the subject emulsion obviates the problem of limited combinations of drug and

carrier inherent in known coprecipitation methods. In contrast to existing melt-fusion techniques, the present method does not require the application of high temperatures which can inactivate or decomposed solubilized compounds. Further, the method of the present invention is applicable to solid/oil combinations in which the oil phase can be utilized to solubilize a lipophilic compound. Melt-fusion methods and coprecipitation methods have not been described for the production of multiple emulsions.

The methods and compositions described herein will be useful in a wide range of emulsion applications and will be particularly attractive for applications in the pharmaceutical, food and cosmetics industries.

Summary of the Invention

This invention provides methods and compositions which are useful for the preparation of stable emulsions. More particularly, glass compositions comprising a water-soluble, non-surface active matrix compound and an oleaginous material from which emulsions can be readily formed by contacting the glass with an aqueous phase are provided. The glasses of the present invention are designated self-emulsifying glasses. Emulsion and multiple emulsion compositions including, among others, oil-in-water emulsions and water-in-oil-in-water emulsions are provided. A variety of water-soluble and/or lipid soluble active

ingredients can be introduced into the self-emulsifying glasses and emulsion compositions of the present invention employing the methods and compositions described hereinafter.

The self-emulsifying glasses of the present invention are useful for the generation of emulsions and multiple emulsions, particularly oil-in-water emulsions and water-in-oil-in-water emulsions. The subject self-emulsifying glasses are particularly useful in pharmaceutical, food and cosmetic applications to form emulsions which do not contain surfactants or which avoid the use of multiple surfactants. The compositions and methods of the present invention are also particularly useful in applications which require stable multiple emulsions. The subject glasses can be stored under appropriate storage conditions for long periods without loss of emulsion-forming capability. Emulsions can be generated from the glass when needed by contact with an aqueous phase suitable for the desired application. The subject self-emulsifying glasses are also useful as drug delivery agents, to be incorporated in capsules, tablets or other dosage forms for oral administration to humans or animals, as a means for delivery of pharmaceutical agents or other active ingredients.

The stable water-in-oil and oil-in-water emulsions produced from self-emulsifying glasses of the present

invention do not require art-recognized surfactants or emulsifying agents. The matrix compounds of the present invention are not surface active agents, surfactants or emulsifying agents. The stable multiple emulsions, e.g., water-in-oil-in-water emulsions, of the present invention require a stable water-in-oil emulsion, preferably a water-in-oil emulsion including an emulsifying agent, but do not require a second water-soluble surfactant to obtain the multiple emulsion. Avoiding the use of surfactants is beneficial, particularly in pharmaceutical, food and cosmetic applications, because of their potential for toxic, irritant or allergic effect. Avoiding the use of a second surfactant in multiple emulsions avoids the problem of surfactant mixing or migration which can limit the stability of multiple emulsions.

Emulsion compositions produced from the subject self-emulsifying glasses can generally be employed in any application for which emulsions or multiple emulsions are recognized to be useful. In general, emulsions are employed to carry, transport, deliver, or protect active ingredients or alternatively to separate and isolate a desired component from a mixture or remove an undesirable component from a mixture. The subject emulsions are useful in all such general applications of emulsions and multiple emulsions.

Among others, monosaccharides, disaccharides and non-sugar sweeteners such as cyclamates, saccharines and water soluble polymers including polyvinylpyrrolidones (PVP), cellulose derivatives and maltodextrins function as matrix compounds in the formation of the self-emulsifying glasses of the present invention. Saccharides including but not limited to sucrose, fructose and trehalose function as matrix compounds in the subject glasses. Preferred non-polymeric matrix compounds are molecules which taste-sweet, more preferred are molecules which are at least about as sweet as sucrose. Saccharides, monosaccharides, disaccharides, sugar alcohols and sugar derivatives, like chlorinated sugars which are at least about as sweet as sucrose are useful as matrix compounds in the present invention. Non-sugar sweeteners useful as matrix compounds include various sweet-tasting molecules including but not limited to amino acids, amino acid derivatives, Aspartame (Trademark) and derivatives thereof, and sulfamates including cyclamates, saccharines, acesulfams and derivatives thereof.

Non-polymeric molecules that posses a tripartite glucophore comprising three structural features: a polarized bond or proton donor, an electronegative atom, and a region capable of hydrophobic bonding or dispersive bonding are of use as matrix compounds in the self-emulsifying glasses prepared using the solvent methods of the present invention. Molecules possessing a tripartite

glucophore having the three structural features of a proton donor, an electronegative atom and a hydrophobic region are of particular use as matrix compounds in the solvent-based methods of preparation of glasses of the present invention. Molecules possessing such tripartite glucophores are of particular use in glass preparation methods which employ water as a solvent.

Polymeric matrix compounds that are useful in self-emulsifying glasses of the present invention include among others PVPs, maltodextrins and cellulose derivatives. Crosslinked and non-crosslinked PVPs ranging in molecular weight from about 15 to 70 thousand can be processed by the methods described herein to form self-emulsifying glasses. Water-soluble cellulose derivatives including carboxymethylcellulose and hydroxyalkycelluloses including hydroxmethyl- and hydroxypropylcelluloses can be processed by the methods described herein to form self-emulsifying glasses. Maltodextrins of the present invention are dextrose copolymers with starch, classified as having dextrose equivalents from about 5 to about 25. Both agglomerated and non-agglomerated forms of maltodextrin function in the compositions and methods of the present invention.

In general, the various matrix compounds can be admixed to form glasses of the present invention. Employing a mixture of matrix components can, for example, lead to

self-emulsifying glasses with higher glass transition temperatures. The higher the glass transition temperature, the more kinetically stable the glass. Glasses with higher glass transition temperatures will be generally more stable to storage and have longer shelf-lives. It is generally preferable that glass transition temperatures be about 20°C or more above room temperature. Mixtures of non-polymeric matrix compounds, such as sucrose, with polymeric matrix compounds, such as maltodextrin, result in glasses with higher transition temperatures compared to glasses formed with the non-polymeric matrix compound alone. In particular, the use of a mixture of sucrose and maltodextrin as the matrix compound results in glasses having higher glass transition temperature than sucrose-based glasses. Specifically, a mixture of sucrose and 3% by weight maltodextrin when combined with mineral oil and processed by the solvent method described herein results in a self-emulsifying glass having a glass transition above about 180°C.

Oleaginous materials useful in the compositions and methods of the present invention include a variety of oils, particularly those which are in liquid form at about room temperature. Oils useful particularly in pharmaceutical, cosmetic or food applications of emulsions and glasses include but are not limited to fluorodecalin, mineral oil (heavy or light), vegetable oil, peanut oil, soybean oil, safflower oil, corn oil, olive oil, oil components thereof,

and mixtures thereof. Oleaginous materials also include water-in-oil emulsions, i.e., in which the oil phase is the external phase of the emulsion and which posses the bulk properties of an oil. The aqueous phase of the water-in-oil emulsion can incorporate a water-soluble active-ingredient. The oil phase of the water-in-oil emulsion can incorporate a lipid-soluble active ingredient. In general, any type of water-in-oil emulsion, produced by any known process and containing any surfactant useful for producing such an emulsion, will function as an oleaginous material in the glasses of the present invention. The methods employed for production of the water-in-oil emulsion must be compatible with any active ingredient that is incorporated therein. Preferred water-in-oil emulsions employ a suitable emulsifying agent, for example a lipid soluble surfactant appropriate for forming a water-in-oil emulsion, including but not limited to those having HLB values less than about 5.5.

It is preferred in the subject self-emulsifying glasses that the weight ratio of the matrix compound to the oleaginous material is at least about 2:1. The weight ratio of matrix compound to oleaginous material is more preferably between about 2:1 and 20:1 and most preferably between about 2:1 and 10:1.

Self-emulsifying glasses are preferably prepared by the solvent method described herein which involves the steps of

combining an oleaginous material with a non-surface active matrix compound, as defined herein, and a sufficient amount of a solvent such that substantially all of the matrix compound is dissolved to form a combination such that the combination is not a stable emulsion followed by removing the solvent from the combination such that a glass results. The solvent employed can include but is not limited to water, aqueous solvents, aqueous alcohols, ethanol, methanol, and organic solvents in which the matrix compound is soluble including among others chloroform. Water and aqueous solvents including aqueous solvents and aqueous alcohols are preferred. Chloroform is, in addition, preferred for use with the matrix compound PVP polymers. In the case in which organic solvents, like chloroform are employed and in which the oleaginous material is not a water-in-oil emulsion, the method can be modified, if desired, to add sufficient solvent to dissolve both the matrix compound and the oleaginous material. The matrix compound and oleaginous material are preferably combined such that the weight ratio of the matrix compound to the oleaginous material is at least about 2:1. Solvent removal is preferably done by evaporation by application of a vacuum accompanied by non-vigorous mixing, i.e., non-emulsive mixing, most preferably by rotoevaporation. The preferred solvent for use in cases in which the oleaginous material is a water-in-oil emulsion is water. Solvent is removed until a dry-appearing solid, solid foam or film is produced. In some cases, rotoevaporation results in

bubbling of the combination and the solid resulting from removal of solvent has the appearance of a solid foam.

Removal of solvent from the matrix compound-oleaginous material combination results in formation of a solid material which is a glass. Glasses formed using non-polymeric matrix compounds or mixtures of polymeric and non-polymeric matrix compounds often retain some level of short or medium range molecular order, designated microcrystallinity herein, as measured by differential scanning calorimetry (DSC). Glasses which are fully amorphous, as measured by X-ray diffraction and DSC can be prepared by the solvent method described herein. Fully amorphous glasses may be very hygroscopic and the absorption of significant amounts of water into glasses is detrimental to their functionality and shelf-life. Thus, glasses retaining some level of microcrystallinity, from about 10% to 60% microcrystallinity as measured by DSC, are preferred. The subject glasses do not retain more than about 10% long range molecular order as measured by X-ray diffraction.

In the cases in which non-polymer is employed in the matrix compound, it is preferred that the solvent be removed at a rate that is fast enough to prevent the formation of significant, i.e., greater than about 10%, long range molecular order via crystallization of the non-polymer component of the matrix compound. This can

generally be achieved if the rate of solvent removal is faster than the rate of crystallization of any matrix component from the solvent solution.

The process steps can in many cases be performed at about room temperature. It is preferred that the process steps are performed at the lowest temperatures possible which allow generation of a dry appearing solid. It is more preferred that the process steps are performed at temperatures less than about 50°C. In the solvent method, the process steps should be performed to avoid melting or decomposition of the matrix compound, i.e., the process should be performed at temperatures less than about the melting point or decomposition point of the matrix compound. Many, if not all, matrix compounds will have melting points below about 140°C. In cases in which an active ingredient is to be incorporated in the self-emulsifying glass process steps should preferably be performed at temperatures which ensure that the active ingredient will not decompose or be significantly inactivated.

Lipid soluble active ingredients can be incorporated into the self-emulsifying glasses by being added to the oleaginous material prior to or simultaneously with its combination with the matrix compound. Water-soluble active ingredients can be incorporated into the self-emulsifying glasses of the present invention in the aqueous phase of a

water-in-oil emulsion oleaginous material. The water-in-oil emulsion must be formed prior to its combination with the matrix compound.

Emulsions and multiple emulsions are prepared from the self-emulsifying glasses of the present invention by addition of a sufficient amount of an aqueous phase such that the desired type of emulsion, e.g., oil-in-water, water-in-oil or water-in-oil-in-water is formed. Suitable aqueous phases depend on the desired emulsion application and include but are not limited to acidic or basic aqueous solutions with pH ranging from about 1 to 10 and aqueous alcohol having an alcohol content less than about 95% (v/v). The subject emulsions are generated by simply contacting the self-emulsifying glass with the aqueous phase. No mixing is necessary to generate the emulsion from the glass.

Active ingredients that are chemical reactants, chelating agents, catalysts, enzymes, biological cells, pharmaceutical agents, cosmetic and personal care agents including sunscreens, antiperspirants, hypoallergenic agents and the like, and food additives including flavoring agents, coloring agents, perservatives and the like can be introduced into the self-emulsifying glasses and emulsion compositions of the present invention. Pharmaceutical agents useful in the compositions of the present invention include but are not limited to peptides, proteins, vaccines, therapeutic enzymes, therapeutic antibodies, hormones, antimicrobial agents, lipoxygenase inhibitors, acyl transferase inhibitors, chemotherapeutic

agents, anticoagulant agents, thrombolytic agents or colony stimulating factors. More specifically pharmaceutical agents include but are not limited to dismutases, erythropoietins, interferons, interleukins, monoclonal antibodies, tumor necrosis factors, human growth hormone, insulin, ceftriaxone, cephalosporins, acetaminophen, a beta-blocker, trandate, labetol, 5-fluorouracil, methotrexate, mechlorethamine HCl, urease, LH-RH analogs, analogs of gonadotropin-releasing hormones. The methods and compositions of the present invention are particularly useful in the preparation of drug delivery agents for such pharmaceutically active ingredients.

The methods and compositions described herein can be employed to improve the means of delivery of pharmaceuticals by protecting a patient from deleterious effects of pharmaceuticals for example those having an unpleasant taste, a general irritant effect, a gastrointestinal irritant effect, or a toxic effect. The methods and compositions described herein can also be used to generally protect active ingredients from decomposition or inactivation. For example, moisture-sensitive and/or oxygen-sensitive active ingredients can be protected. Water-soluble active ingredients are introduced into the aqueous or water phases of the subject emulsions. Lipid-soluble active ingredients are introduced into the oleaginous or oil phases of the subject inventions.

The methods of the present invention do not require the application of high temperatures to produce the subject glasses. The methods and compositions of the present invention are consequently particularly useful with any water-soluble or lipid-soluble temperature sensitive active ingredients. The methods of the present invention are of more particular use with active ingredients which are partially or fully inactivated, or decompose at temperatures above about 50°C.

Brief Descriptions of the Figures

Figure 1 is a graph of turbidity as a function of time (minutes) obtained from absorbance measurements at 400 nm. The graph compares turbidity of two oil-in-water emulsions produced from self-emulsifying glasses: one having water as the external phase (solid diamonds) and one having normal saline as the external phase (open squares) with a dispersion of a physical mixture of the same components (solid squares). The self-emulsifying glasses were prepared using sucrose and mineral oil in a 6:1 weight ratio. The dispersion was prepared by vortexing (20 min.) a physical mixture of sucrose, mineral oil and water having the same relative composition as the emulsions. All measurements were made at 25°C. The decrease in turbidity in the dispersion signals cracking of the emulsion, since it was accompanied by phase separation. No phase separation was observed during the course of the experiment with the

two emulsions, so the decrease in turbidity observed is attributed to decreasing emulsion particle size.

Figure 2 is a graph of conductivity of an emulsion formed from a self-emulsifying glass as a function of the weight content. Water content is expressed as the weight% of water of the emulsion. Conductivity is expressed as conductivity relative to water. All measurements were at 25°C. The self-emulsifying glass contained sucrose and mineral oil in the weight ratio 4:1.

Figure 3 is a graph of viscosity of an emulsion with a sucrose to mineral oil weight ratio 6:1 at 25°C as a function of shear rate in rpm. Measurements were made as a function of both increasing shear rate, open squares, and decreasing shear rate, closed diamonds.

Figure 4 is an X-ray diffractogram of a sucrose-mineral oil self-emulsifying glass produced by the solvent method of the present invention. The diffractogram of the glass, trace B, is compared to a diffractogram of a physical mixture of sucrose and mineral oil, trace A.

Figure 5 is a comparison of differential scanning calorimetry thermograms for self-emulsifying glasses which form W/O/W emulsions on contact with an aqueous phase. Thermogram A is of a glass prepared using a mixture of sucrose and maltodextrin (3% by weight, mixture designated

White Di-Pac) as the matrix compound. Thermogram B is of a glass prepared using sucrose as the matrix compound. The graph displays normalized heat flow (Watts/gram) as a function of temperature (°C).

Detailed Description of the Invention

An emulsion is a dispersion of one immiscible liquid in another with the dispersed liquid in the form of droplets. In general, the diameter of the dispersed droplets exceed 0.1 microns (see: P. Becher (1983) Encyclopedia of Emulsion Technology Vol. 1, p. 108). The dispersed liquid is the internal phase (or discontinuous phase) and the other liquid is the external phase. Emulsions are most typically employed with an aqueous phase and an oil phase. In a water-in-oil emulsion, an aqueous phase is dispersed in an oil phase. In an oil-in-water emulsion, an oil phase is dispersed in an aqueous phase. Emulsions are inherently unstable; The internal phase will coalesce with time and the emulsion will crack. It has been generally accepted that an emulsifying agent (surfactant) is required to stabilize an emulsion. Thus, conventional stable emulsions contain at least one emulsifying agent.

The type of emulsion (water-in-oil or oil-in-water) can be determined in several ways. An emulsion will typically have the bulk appearance of its external phase, i.e., a W/O emulsion has the appearance of an oil, an O/W emulsion has

the appearance of water. Several more quantitative methods for determining the type of emulsion are dye solubility tests (a water-soluble dye tints an O/W emulsion, but not a W/O emulsion) and electrical conductivity tests (a W/O emulsion generally does not conduct an electric current).

Multiple emulsions are more complex types of emulsions in which the dispersed droplets contain smaller dispersed droplets of an immiscible liquid. A water-in-oil-in-water (W/O/W) emulsion contains droplets of an oil in an external aqueous phase and the droplets of oil contain smaller droplets of an internal aqueous phase. The external and internal aqueous phases may be the same or different. Multiple emulsions have been prepared by emulsifying a primary O/W or W/O emulsion (see: Davis and Walker (1987) Multiple Emulsions as Targetable Delivery Systems Meth. Enzymol. 149:51-64). The formation of multiple emulsions has generally been believed to require the use of two surfactants having different HLB values (see: Davis and Walker, 1987; Florence and Whitehill (1981) J. Colloid Inter. Sci. 79:243-256; Martin et al. Physical Pharmacy Physical Chemical Principles in the Pharmaceutical Sciences, Lea & Febiger, Philadelphia, PA pp. 553-565; Frenkel et al. (1983) J. Colloid Inter. Sci. 94:174-178; Garti et al. (1983) J. Dispersion Sci. Technol. 4:237-252). Surfactant migration, i.e., the migration of surfactants with two different HLB values throughout the phases, is thought to occur in multiple emulsion systems utilizing

more than one emulsifying agent (Frenkel et al., 1983). Surfactant migration results in disruption of the multiple emulsion. W/O/W emulsions typically are stable for 24 to 48 hrs (Florence and Whitehall, 1981), however, under extreme conditions, stabilities up to 30 days have been achieved (Davis and Walker, 1987 and Garti et al., 1983).

The emulsions and multiple emulsions of the present invention are generated by addition of a selected aqueous phase to a self-emulsifying glass. The self-emulsifying glass is prepared by combining a water-soluble, non-surface active matrix compound with an oleaginous material which can simply be an oil phase optionally containing a dissolved lipid-soluble active ingredient or a primary emulsion, for example a water-in-oil emulsion optionally containing a dissolved active ingredient.

The self-emulsifying glasses of the present invention form emulsions on contact with a sufficient amount of an aqueous phase. Emulsion formation is almost immediate, requiring no significant energy input. The emulsion can be formed from the subject glasses by simply contacting the solid with an aqueous phase. This characteristic of the glass avoids process steps involving emulsive mixing such as agitation, homogenizing, microfluidizing, ultrasonication or processing in a colloid mill. Unlike prior art self-emulsifying systems (Pouton (1985) Int'l J. Pharmaceutics 27:3335-348) or dried emulsions, the subject

glasses which are precursors to simple emulsions contain no art-recognized surfactant. The self-emulsifying glasses which are precursors to multiple emulsions at most require a surfactant to form the primary emulsion.

Simple two phase emulsions and multiple (i.e., three phase) emulsions can be prepared employing the self-emulsifying glasses described herein. A self-emulsifying glass precursor to a W/O/W emulsion is prepared from a mixture of a primary water-in-oil emulsion and a water-soluble, non-surface active carrier. The multiple emulsion can be formed from the glass on contact with an aqueous phase.

The self-emulsifying glasses of the present invention can incorporate active ingredients such as pharmaceutical agents, reactive chemical agents, dyes, flavoring agents and the like, and can function as a vehicle for the delivery or solubilization of such active ingredients.

Lipid soluble active ingredients can be incorporated into the oleaginous material of the glass. Water soluble active ingredients can be incorporated into self-emulsifying glasses in the aqueous phase of the water-in-oil emulsions.

The self-emulsifying glasses of the present invention are prepared as solids, preferably as dry, non-oily solids. The glasses can be in the form of a powder, a solid foam or

a film. The glass can be stored, if protected from extremes of humidity, for extended periods without loss of emulsion forming capability.

In contrast to crystalline materials, glasses and liquids have only short-range molecular order. For example, in crystals the nearest neighbor separations and bond angles are exactly equal while in a glass, the nearest neighbor separations are approximately equal over a few molecular distances. Practically this results in an inability to predict the location of a neighbor within the glass. As a result, crystallizing material may be differentiated easily from glasses by X-ray diffraction methods. A glass or liquid can only produce weak and diffuse diffraction effects, while crystallites can give strong and sharp diffraction effects. In this sense, a glass is also amorphous to X-ray diffraction (G. O. Jones, "Glass," Wiley, New York, NY, 1971, pp. 5-8). Since the first amorphous materials to be studied in detail were prepared by cooling a melt, the terms "glass" or "glassy" have become synonymous in the literature with amorphous solids. In fact, recent literature citations refer to amorphous materials as glasses even when prepared by spray-drying and lyophilization (G. W. White and S. H. Cakebread, J. Fd. Technol., 1:73-82 (1966)).

Although glasses characteristically lack long-range order, microcrystalline regions have been detected using

electron microscopy and calorimetric techniques (M. Mathlouthi, Ind. Aliment. Agri., 1279 (1975)). These results indicate that a material may have numerous small discontinuous regions (microcrystalline regions) of crystallinity dispersed among amorphous regions that appear amorphous by X-ray diffraction. The quantity of such regions appear to be dependent on the method of preparation and physical properties of the respective materials.

The self-emulsifying glasses of the present invention are amorphous materials as measured by X-ray crystallographic techniques. Materials having about 10% (by weight) or less long range crystallinity appear to be amorphous by X-ray methods. Certain of the glasses of the present invention appear to contain regions of microcrystallinity as measured by differential scanning calorimetry (DSC). The extent of microcrystallinity in a glass can vary significantly from essentially no microcrystallinity up to about 60% (by weight) microcrystallinity. The extent of microcrystallinity appears to depend on the extent of crystallization of components that occurs during processing of the glass. It has been found, for example, that glasses having little or no measurable microcrystallinity an be prepared by the solvent method of the present invention if siliconized glassware is employed during solvent removal. Within a wide range, the extent of microcrystallinity in the glass does not effect the ability of the glass to form emulsions on contact with a aqueous phase. It has been

found that the glass having very low microcrystallinity levels can be very hygroscopic. Thus, for certain applications requiring, for example, storage of the self-emulsifying glass, it is preferred that at least some low level of microcrystallinity be present in the glass. Glasses having a microcrystallinity of at least about 10% to about 60% (by weight) are preferred with glasses having about 20-30% microcrystallinity being more preferred.

The self-emulsifying glasses of the present invention are distinct from prior art dried emulsions and concentrated emulsions, since these compositions result from an existing stable emulsion which typically contains at least one emulsifying agent. Thus, existing dried emulsion precursors contain art-recognized surfactants. Similarly, existing dried multiple emulsion precursors are distinct from the glasses of the present invention in that they are derived from formed multiple emulsions and contain at least two surfactants.

The matrix compounds of the glasses of the present invention are water soluble, non-surface active compounds. Two classes of matrix compounds have been identified which can be employed to produce self-emulsifying glasses. One class includes monosaccharides and disaccharides, such as sucrose, trehalose, and fructose, sweeteners including on-saccharide sweeteners and synthetic sweeteners, such as cyclamates and saccharines. The other class of matrix

compound includes water-soluble polymers such as polyvinylpyrrolidones, water-soluble cellulose derivatives and maltodextrins. Mixtures of two or more of the various matrix compounds can also be employed to produce self-emulsifying glasses.

In general a "sweetener" is any material that tastes sweet. As used herein, the term sweetener is specifically intended to encompass sugars as well as molecules, compounds or mixtures other than sugars which taste sweet. Sweeteners include non-saccharide sweeteners, like sugar-alcohols, amino acids and sulfamates among many more. Non-saccharide sweeteners can be naturally-occurring compounds, e.g., sugar-alcohols and amino acids, or synthetic sweeteners, e.g., chlorinated sugars, Aspartame (Trademark for aspartylphenylalanine methyl ester), cyclamates or saccharines. Preferred sweeteners for use as a matrix compound in the solvent method of the present invention are those compounds or mixtures that are at least about as sweet as sucrose. It is preferred, at least for applications in the pharmaceutical, food and cosmetic fields that a matrix compound be non-toxic.

In non-polymeric matrix compounds, an empirical correlation between the sweetness of a molecule and the ability to produce a self-emulsifying glass employing that matrix compound has been discovered. It was found that the glasses produced using sucrose and oils (i.e., mineral oil)

did not taste sweet. This suggested that the formation of a self-emulsifiable glass somehow interfered with taste reception. It was found that self-emulsifying glasses could be produced by the methods described herein from intensely sweet-tasting molecules, sweeteners such as cyclamates and saccharines. This suggested that the regions or structural features of a molecule associated with the perception of sweetness (as assayed by human taste) were correlated with the ability to form self-emulsifying glasses by the methods described herein using water as the solvent.

It has been found that self-emulsifying glasses could not readily be formed with glucose, lactose, maltose and the sugar alcohols mannitol and sorbitol, using water as a solvent. Lactose is significantly less soluble in water and sufficient lactose cannot be solubilized in water to allow glass formation via rotoevaporation. Glucose, mannitol and the sugar alcohols appear to have sufficient water solubility, but it was found that a dry solid glass could not be produced via rotoevaporation. It was found that self-emulsifying glasses could be produced from trehalose. The resultant trehalose-based glasses, however, did not appear to be dry solids. Glucose, maltose, lactose, sorbitol, mannitol and trehalose are all reported to be less sweet-tasting compared to sucrose. Thus, there is an apparent correlation between the intensity of sweetness, compared to sucrose, of a potential matrix

compound and the ability to produce a self-emulsifying glass employing that matrix by the water solvent method described herein.

There have been many attempts to correlate the property of sweet-taste to molecular structure (see: Kier (1972) J. Pharmaceutical Sci. 61:1394-1397 and a recent review Lee (1987) Adv. Carbohydrate Chem. and Biochem. 45:199-351, both of which are incorporated by reference in their entirety herein). A straightforward correlation has not been identified, because of the diversity of types and structures of molecules that are sweet. A brief summary of the classes of molecules that are sweet and a general ranking of intensity of sweetness is provided in Birch (1987) Endeavour 11:21-24. Sweet molecules are found among sugars; sugar derivatives: including hydrogenated, deoxy, anhydro and chlorinated sugars; amino acids; amino acid derivatives: including Aspartame (Trademark) and chlorinated amino acids; sulfamates including: saccharines, cyclamates and acesulfams; aminonitrobenzenes; dihyrochalcones; isocoumarines; certain proteins and peptides such as thaumatin and hernadulcin. Not all compounds of a particular type will be sweet and the intensity of sweetness among apparently similar compounds can change significantly. In some cases, only one of a pair of enantiomers will be sweet-tasting. No general correlation of sweetness with a particular physical or chemical molecular property has been established. Certain

correlations between the intensity of sweetness and physical or chemical properties have been established within the limits of closely related compounds. It has been reported, for example, that the sweetness of sugars correlates with their water solubility and that the sweetness of aminonitrobenzenes correlates with their melting points (see Lee (1987) p. 206). Such limited correlation suggest that properties related to weak interactions, such as hydrogen bonding or hydrophobic and hydrophilic interaction may be in part responsible for sweet taste. Most recent theories of sweetness are based on the concept of a sweetness receptor which will bind to molecules having a particular three dimensional structure or arrangement of certain types of chemical moieties. A concept that rationalizes the sweetness of a variety of sweet-tasting molecules and relates sweetness to a three-dimensional structure involves a tripartite glucophore (see Lee, 1987, p. 231 and Kier, 1972). The tripartite glucophore is a structural feature associated with sweetness which consists of a polarized bond, designated AH or A, an electronegative atom, designated B and a third feature. Initially two structural features: a proton donor or more generally a polarized bond and an electronegative atom separated in space by about 2.5 to 4.0 Å were described as minimally required for sweet taste (Shallenberger and Acree (1967) Nature 216:480). Examples of AH include O-H groups, N-H groups and C-H groups of cycloalkyl groups or aromatic rings. Examples of B include

oxygen atoms, oxime groups, nitro groups, carbonyl groups, and S-O or SO_2 groups. The AH, B unit in the cyclamate and saccharin sweeteners are assigned to the NH-SO_2 moieties. The third feature, designated X herein, is associated with increasing intensity of sweetness. The X feature is described specifically as a lipophilic region or hydrophobic bonding area (Deutsch and Hansch (1966) Nature 211:75), or more generally as a region capable of dispersive bonding or a region susceptible to electrophilic attack (Kier, 1972). Examples of the X feature include alkyl and alkenyl groups, cycloalkyl and cycloalkenyl groups, aromatic rings, the C-2 substituent in aminonitrobenzenes. All three features are described as involved in binding of the sweet molecule to the receptor. The features of the tripartite glucophore form a triangle with the AH-B distance ranging from about 2.5-4.0 Å, the AH-X distance ranging from about 3.1 to 5.2 Å and the B-X distance ranging from about 5.2 to 7.4 Å. The triangular tripartite glucophore structure is more narrowly depicted with a AH-B distance of about 2.6 Å, a B-X distance of about 5.5 Å and a X-AH distance of about 3.5 Å. Intensity of sweetness is associated with better fit or improved binding in the receptor. Sweet-tasting compounds which possess a tripartite glucophore, particularly in which the X feature is a region capable of hydrophobic bonding, are useful in the preparation of self-emulsifying glasses via the water solvent method as described herein. Those compounds possessing the tripartite glucophore which are

sweeter than sucrose are preferred matrix compounds for use in the compositions and methods of the present invention.

Sweetness is generally compared to that of sucrose. An extensive literature exists in the flavor and fragrance art on the methods of detecting and comparing flavors, including sweetness. Method for testing the relative sweetness of particular compounds are well-known in the art. Qualitative sweetness evaluation can simply be performed by individual taste-tests of solids or aqueous solutions. Care should be taken, however, in making such taste tests, since certain sweet compounds may be toxic. Taste-tests by a single individual may not be definitive due to partial taste-dysfunction or aberrations in an individual's sense of taste from the norm. Quantitative tests comparing relative sweetness of compounds are generally performed by special test-panels. The intensity of sweetness is often ranked compared to sucrose by determination of the concentration of an aqueous solution that will be iso-sweet with an aqueous solution of a known concentration of sucrose. A variety of literature sources are readily available which provide quantitative rankings of the sweetness of a variety of compounds (See, for example, Grant and Hatch's Chemical Dictionary (1987) 5th (and later) Editions, Grant and Grant, eds., McGraw-Hill, New York; Andres (1977) Low Calorie and Special Dietary Foods, CRC Press)

It is important that the lipophilic region of the tripartite glucophore, or more correctly the lipophilic surface of sucrose, saccharin or cyclamates, not be confused with classical lipophilic region of emulsifying agents, e.g., long chain hydrocarbons.

The second type of matrix compounds are polymers which are not sweet-tasting. These materials appear to have some structural similarity to some of sweet materials but no clear correlation between the structure of the polymers and their utility in self-emulsifying glasses is known. Polymeric matrix compounds include but are not limited to polyvinylpyrrolidones including members of that group containing any number of vinyl groups, water-soluble cellulose derivatives, both fully and partially derivatized, including among others carboxymethylcellulose and hydroxyalkylcellulose, and maltodextrins which are starch/dextrose copolymers.

There are no size or molecular weight restrictions on matrix compounds as long as they remain water-soluble and non-surface active. Matrix compounds, in general, are chosen to be compatible with the oleaginous material, solvent and aqueous phase components of the formulations.

Since the polymeric matrix compounds of the present invention do not taste-sweet, it is clear that the

correlation between sweetness and the presence of a tripartite glucophore and the functionality of a compound for emulsion formation is not absolute, i.e., sweetness is sufficient but not required for matrix compounds that function in the formation of self-emulsifying glasses. The correlation between intensity of sweetness and function as a matrix compound in the present invention is useful for selecting candidate matrix compounds which can be readily assessed for suitability for use in the methods of the present invention by following the procedures described herein.

Surface active agents or emulsifying agents are molecules that are preferentially adsorbed at interfaces. For aqueous systems, the adsorption or accumulation of emulsifying agents at the water/air interface sharply lowers the surface tension of water (see Becher, 1983, p. 111). Accumulation of surface active agents occurs lowering the surface tension until the water/air interface is saturated with the emulsifying agent, i.e., the plateau region. Once the surface is saturated with the emulsifying agent, additional emulsifying agent results in the formation of associated structures or micelles. Emulsifying agents reduce the surface tension by orientating at the water/air interface such that the non-polar region of the molecule is exposed to the air (relatively non-polar). The hydrophilic portions of the molecule tend to orientate towards the water. The three

basic structural requirements for emulsifying agents are (i) lipophilic region, (ii) hydrophilic region, and (iii) a balance between the lipophilic and hydrophilic regions. It is important that there be a balance between the hydrophilic and lipophilic regions. For example, if a molecule is too hydrophilic it will locate where the water is located, i.e., in the bulk. Conversely, if a molecule is too lipophilic it may be completely expelled from the aqueous phase. The lipophilic region is commonly recognized as the hydrocarbon chain part of the molecule. These lipophilic regions may be either saturated or unsaturated hydrocarbon chains or, less commonly, heterocyclic or aromatic ring systems. In practice, emulsifying agents are commonly found to have hydrocarbon chains from eight to eighteen methylene groups. The hydrophilic regions are characterized as to whether or not the region is anionic, cationic or non-ionic.

This invention describes the use of certain molecules and classes of molecules that are not predicted to be surface active by conventional emulsification theory. These molecules and classes of molecules, designated matrix compounds herein, do not significantly decrease the surface tension of aqueous solutions and thus are not reported or anticipated to form associated structures, i.e., micelles. According to conventional understanding, the matrix compounds of this invention lack two of the three required structural requirements of emulsifying agents, namely a

lipophilic region and therefore a hydrophilic/lipophilic balance. Matrix compounds of the present invention are therefore expected to be equally dispersed between the interface and the bulk (Hem et al. (1986) in "The Theory and Practice of Industrial Pharmacy", Third Edition, Lachman et al. Eds., Lea & Febiger, Philadelphia, PA, p. 104). For example, sucrose is a matrix compound of the present invention. A sucrose molecule is regarded as a hydrophilic group and not surface active (J. G. Riess et al., Biomat., Art., Cells, Art., Org., 16:421-430 (1980)). This is evidenced by the fact that, surfactants are prepared from sucrose by esterification (mono- and diesters) with long chain fatty (a hydrocarbon region) acids such as stearic ($C_{18}H_{36}O_2$) and cocoaic acids ($C_{18}H_{16}O_4$) which provide a lipophilic region and thus surface activity.

The term "self-emulsifying" as used herein has been applied to glasses formed from matrix compounds and an oleaginous material. The term refers to the emulsion-forming property of the glass and specifically to the ability to form an emulsion by simply contacting the glass with an aqueous phase.

The oleaginous material of the present invention is a material that containing oils or glycerides and esters of fatty acids. The oleaginous material is preferably liquid

at about room temperature. Such oils include but are not limited to natural and synthetic oils, mineral oil, vegetable oil, peanut oil, safflower oil, olive oil, corn oil, soybean oil, castor oil, linseed oil, petroleum and components thereof, fish oils and oils of animal origin, and fluorodecalins, including perfluorodecalin. The oleaginous material can include flavor oils, such as oils of spearmint, peppermint, wintergreen and the like. It is, however, preferred that a flavor oil is not the major component of the oleaginous material. The oil is selected to be appropriate for a given application and to be compatible with other components in an emulsion formulation. While some naturally occurring oils may contain small amounts of monoglycerides or other compounds that can act as emulsifying agents, these materials are not required to generate the emulsions of the present invention.

Oleaginous materials also include water-in-oil emulsions. Such emulsions have bulk properties like an oil, specifically like the oil phase of the emulsion. The W/O emulsions contain an aqueous phase dispersed within the oil phase. The oil phase can include any of the oleaginous materials listed hereinabove. The aqueous phase can be water, aqueous salt solutions, acidic or basic aqueous solutions (pH 1-10) and aqueous alcohol solutions. The W/O emulsion can be prepared by any art-know technique and may include an emulsifying agent suitable for stabilizing the

W/O emulsion. Preferably, the W/O emulsion contains a lipid-soluble surfactant having an HLB value less than about 5.5. The amount of surfactant added to generate the water-in-oil emulsion depends on the oil phase and aqueous phase that are to be dispersed.

The "solvent" used in the methods described herein means any liquid having the capacity to solubilize the matrix compound. The solvent must, however, be volatile in that the solvent must be removable from the matrix compound/oleaginous material combination by application of a vacuum without application of high temperatures. It is preferred that process temperatures be maintained below about 50°C. Solvents can include but are not limited to water, aqueous alcohols, alcohols, acidic and basic aqueous solutions and organic solvents, like chloroform. Water and aqueous solutions are preferred solvents for all matrix compounds. In addition, chloroform is a preferred solvent for PVPs. Water is the preferred solvent for processing of self-emulsifying glasses which contain water-in-oil emulsions. The solvent is chosen to be suitable for the desired application, keeping in mind that residual levels of solvent can be retained in the self-emulsifying glass and product emulsions, and to be compatible with the other components of the formulation.

The "aqueous phase" is added to the self-emulsifying glass to generate an emulsion. The aqueous phase can

solubilize the matrix compound. The aqueous phase must contain water and is preferably at least about 5% by weight water. The aqueous phase can include but is not limited to neutral, acidic and basic aqueous solutions preferably ranging in pH from 1-10, and organic compounds that are soluble in or miscible with water. The aqueous phase can contain such organic compounds, alone or as a mixture with each other, in combination with water. The aqueous phase is selected based on the desired application and to be compatible with the other components of the formulation.

"Active ingredients" as used herein refers to the compound of interest which is optionally carried, or solubilized, in one of the phases of the emulsions. An active ingredient can be water-soluble or lipid-soluble. Lipid-soluble active ingredients can be solubilized in the oleaginous material including the oil phase of the primary emulsions employed as oleaginous materials. Water-soluble active ingredients can be solubilized in any external or internal aqueous phase of the emulsions of the present invention. Active ingredients include among others chemical reactants, catalysts, including enzymes and biological cells, inks, dyes, chelating agents, complexing agents, pharmaceutical agents, food additives, flavoring agents, colorants, cosmetic agents. Pharmaceutical agents include among others human and animal pharmaceuticals, therapeutic enzymes, peptides, proteins, therapeutic and diagnostic antibodies, vaccines, recombinant peptides or

proteins, analgesics, chemotherapeutic agents, and enzyme inhibitors. The amount of active ingredient in the emulsion or self-emulsifying glass is selected to be appropriate for the desired application. The amount introduced into the formulation is limited by the solubility of the ingredient in the aqueous or oil phase. In general, the other components of the formulation will be chosen to be compatible with the active ingredient. Similarly, any process steps employed in the preparations of glasses and emulsions containing active ingredients must be compatible with substantially retaining the activity of the active ingredient.

Emulsions and multiple emulsions are employed to carry, transport, protect or separate active ingredients. Emulsions can be employed to protect moisture- or air-sensitive compounds and to protect active ingredients from chemical or biological inactivation. Emulsions can also mask harsh or unpleasant tastes in pharmaceutical or food emulsions or can protect a patient from irritant or toxic effect of an active ingredient. Emulsion can be used to isolate a desired component from a mixture or remove an undesirable or waste product from a mixture.

Although not wishing to be held to any particular theory, it is believed that the self-emulsifying glasses of the present invention comprise a matrix formed by a water-soluble, non-surface active compound, the matrix compound,

throughout which an oleaginous material is dispersed. The solvent method for producing an self-emulsifying glass described herein is, thus, believed to allow the formation of a dispersion of a liquid oil in a matrix of a solid.

This invention provides a method for producing self-emulsifying glasses, emulsions and multiple emulsions. As noted above, stable emulsions and stable multiple emulsions are generated by adding an aqueous phase to a self-emulsifying glass. The emulsion can be formed on contact with the aqueous phase and no vigorous mixing or emulsive mixing is required. (The term emulsive mixing relates to vigorous mixing, vortexing, homogenizing, blending, milling and the like which is typically required to produced conventional emulsifier-containing emulsions.) Emulsions and multiple emulsions of the present invention can be formed when desired by adding the aqueous phase to the glass which can be stored without detrimental effect for long periods of time (months) under appropriate storage conditions.

The term "stable emulsion" refers to a liquid-liquid dispersion that is at least more stable over time to cracking or coalescence than a dispersion of the two liquid phases that is prepared (without any emulsifying agents) by vortexing, homogenizing or other emulsive mixing. Dependent on the liquid phases involved a non-stable dispersion will typically coalesce in minutes or over

several hours; Stable emulsions, again dependent on components, will be stable to coalescence for hours or days. A similar meaning is intended when the term "stable" is applied to multiple emulsions. The stable oil-in -water emulsions of the present invention have been observed to be stable to coalescence, phase separation and cracking (if properly stored) over several months. The stable water-in-oil-in-water emulsions of the present invention have been observed to be stable for at least about 90 days.

Stability of oil-in-water or water-in-oil can be monitored experimentally by following changes in turbidity of the emulsion. Such measurements follow particle size in the emulsion. Decreases in turbidity accompanied by visual phase separation indicate cracking of the emulsion. Assessment of the stability of a multiple emulsion is experimentally more complex. Most generally, stability can be assessed as the loss of the internal phase to the external phase, e.g., loss of the internal water phase to the external water phase in a W/O/W emulsion. Stability has been correlated with oil droplet size (Davis et al. (1976) J. Pharm. Pharmacol. Suppl 28:60P) and the size distributions of oil dropets and internal aqueous droplets (Davis and Burbage (1977) J. Colloid Interface Sci. 62:361). Photomicrography can be employed to measure the number and size of multiple internal drops over a period of time to assess stability. Stability can also be assessed by release of certain marker compounds which indicate

disruption of the internal droplets (Magdassi et al., 1984; Florence and Whitehill, 1982; Davis and Walker, 1983). Kita et al. (1977) J. Colloid Interface Sci. 62:87-94 have employed viscosity measurements to estimate the stability of multiple emulsions.

Self-emulsifying glasses of the present invention containing PVP as the matrix compound have been found to be functional even after exposure to the high temperatures and pressures of an autoclave. Emulsions prepared from PVP glasses also were stable to autoclaving. This indicates that at least some of the self-emulsifying glasses of the present invention can be sterilized after preparation with detrimental effect to functionality for emulsion formation.

Self-emulsifying glasses are produced using a solvent method which is believed to result in a glass which is a dispersion of the liquid oil in a solid matrix. The method involves combining a water-soluble, non-surface active matrix compound with an oleaginous material and a sufficient amount of a solvent to dissolve the matrix compound and form a combination. The solvent is then removed from the combination, preferably by application of a vacuum, to give a glass. Solvent removal is preferably done via rotoevaporation. The glass is formed as a solid foam, a film or as a powder on removal of the solvent. The glass can retain some residual level of solvent. An alternative procedure involves adding a solvent that will

dissolve both the matrix compound and the oleaginous material. This method can be applied when PVPs are the matrix compounds and chloroform is employed as the solvent. The alternative method is not useful when the oleaginous material is a water-in-oil emulsion. Water or aqueous solutions are preferred for use when a water-in-oil emulsion is combined with a matrix compound.

In the solvent method of the present invention for preparation of self-emulsifying glasses, a matrix compound is combined with an oleaginous material. It is preferred that the weight ratio of matrix compound to the oil in the oleaginous material be at least about 2:1. The oleaginous material is substantially oil, in cases in which a two phase emulsion system is desired. When the oleaginous material is a water-in-oil emulsion, for example, it will contain substantial amounts of an internal aqueous phase, and can be up to about 30%-40% by weight. The oil in the emulsion oleaginous phase is correspondingly decreased. It is the oil to matrix weight ratio that is important in optimizing the quality of the self-emulsifying glass. When water-in-oil emulsions are the oleaginous phase, the weight ratio of matrix to oleaginous material can be as low as about 1.2:1. When the matrix compound to oil weight ratio is lower than about 2:1, the glass formed by removal of solvent may be coated with residual oil. This residual oil is not necessarily incorporated into the emulsion formed when an aqueous phase is added to the glass. The residual

oil may remain as a separate, non-dispersed phase which can be undesirable for certain application. It is more preferred that the weight ratio of matrix compound to oleaginous material is from about 2:1 to 20:1 and even more preferred that the ratio be between about 2:1 and 10:1.

Preferably solvent is removed from the combination in a way that avoids substantial long range molecular order in the resultant solid, i.e., the resultant solid should be a glass. It is believed that this is achieved if the rate of removal of the solvent is faster than the rate of crystallization of the matrix compound out of the solution. As noted above, regions of microcrystallinity in the glass are tolerated, and even preferred, in the glass without disruption of its self-emulsifying capability. Substantial long range order through crystal formation can affect self-emulsifying capability. It is preferred that the glasses of the present invention contain no substantial long range order. In particular, it is preferred that glasses are amorphous as determined by X-ray diffraction techniques, i.e., that they are less than about 10% by weight crystalline.

Solvent is preferably removed from the combination until a dry-appearing solid, foam or film is generated. In some cases, for example when trehalose is employed as a matrix compound, it may not be possible to obtain a completely dry-appearing solid. A glass having a wet appearance can

give a functional self-emulsifying glass. A material that remains a syrup after extensive solvent removal will not give an emulsion on addition of an aqueous phase. Such syrups were the result of processing of mannitol and glucose by this solvent method employing water as a solvent.

The self-emulsifying glass that results from solvent removal from a combination of a matrix compound and a water-in-oil emulsion has a dry appearance. However, the glass retains an internal aqueous phase which is not removed during solvent removal.

A stable emulsion is not formed during the processing steps of the present invention which result in the self-emulsifying glass. The glass is not a dried emulsion or pre-emulsion as those terms are employed conventionally in the art. The combination formed with the matrix compound and the oleaginous material is not a stable emulsion.

Typically, the processing steps of the solvent method of the present invention can be preformed at about room temperature. Processing is preferably done at temperatures less than about 50°C. Processing using the solvent method avoids the use of high temperatures that can decompose matrix compounds, oils or decompose or inactivate active ingredients. The solvent method avoids temperatures at which the matrix compound melts or decomposes. The method

should be performed below the melting point of the matrix compound. Most matrix compounds of the present invention will melt above about 140°C.

As noted above, the methods and compositions of the present invention are particularly useful when a temperature sensitive active ingredient is employed. As used herein the term "temperature sensitive" relates to any detrimental effect of temperature on an active ingredient including partial or full inactivation, partial or full decomposition or partial or full denaturation. Some active ingredients, particularly some biological materials, will be sensitive even at room temperature. The present method is useful with such active ingredients, since it limits their exposure to higher temperatures.

It is likely that such solid-liquid dispersions can also be produced by combining the liquid oil with a melt of the solid matrix compound, i.e., via a melt fusion process. The combination of a solid melt with a liquid oil is likely to result in a fully amorphous material, lacking any measurable microcrystallinity. Any saccharide, disaccharide, sweetener or sugar alcohol matrix compound of the present invention should produce a self-emulsifying glass when combined with an oleaginous material via a melt fusion process. A melt fusion process should also be applicable to the formation of self-emulsifying glasses

from lactose, glucose, maltose, mannitol and sorbitol which were not successfully processed by the water-based solvent method of the present invention. The melt process has significant disadvantage over the solvent method since rather high temperatures (over about 100°C) must be employed to melt the matrix compound. A melt process is also not preferred for use in the preparation of glasses which contain any temperature sensitive components. Compounds, including PVP, cellulose derivatives or maltodextrins, which decompose on melting (or at temperatures close to the melting point) would not be preferably employed as a matrix in a melt fusion process. The melt process would not be preferred in the production of glasses which incorporate temperature-sensitive active ingredients. Many pharmaceutically active ingredients are inactivated (fully or partially) or decompose at temperatures above room temperature. Many more active ingredients are inactivated (fully or partially) or decompose at temperatures required to melt a matrix compound (above about 100°C, for sugars and sugar alcohols). The melt process can, however, be useful in expanding the range of matrix compounds, at least to the sugars and sugar alcohols, from which a self-emulsifying glass can be prepared. A melt fusion process is, however, not expected to be applicable to the preparation of self-emulsifying glasses that contain water-in-oil emulsions as these primary emulsions are not likely to be stable to the high temperatures required.

Glasses of the present invention can be used in a wide variety of applications, including drug delivery, cosmetics, foods and food additives, personal care products, toxic and hazardous waste treatment, and continuous extraction systems. The present glass can be used to increase solubility of slightly water soluble compounds, to increase absorption of pharmaceuticals, to mask unpleasant tastes, to protect moisture sensitive compounds, to protect water soluble compounds from acidic and basic environments, to prevent gastrointestinal irritation and to reduce toxicity of a variety of compounds.

Glasses of the present invention can be used as delivery agents for many active ingredients which are either lipid-soluble or soluble in aqueous systems, including transferase inhibitors, cephalosporins, chemotherapeutic agents, anticoagulants, thrombolytic agents, colony stimulating factors, dismutases, erythropoietins, human growth hormones, enzymes, vaccines, interferons, interleukins, monoclonal antibodies, peptides, insulin, LH-RH analogs, tumor necrosis factors, factor VIII, epidermal growth factor, insulin-like growth factor, rCD_4, and other drugs.

Embodiments of the present invention are useful as drug delivery agents that also protect active ingredients from

degradation, help limit toxicity, and even to mask unpleasant tastes.

Glasses of the present invention can also be used to deliver peptides and proteins orally, including insulin and LH-RH Analogs, such as leuprolide, analogs of gonadotropin-releasing hormone, which are useful in treating advanced prostatic cancer. The present invention can be used to create stable, solid-phase doses of peptides, including insulin, that can be administered orally, thus obviating the need for injections for hundreds of thousands of patients.

Similarly, the present invention makes stable, solid-phase oral doses available for ceftriaxone, a third generation cephalosporin which is the drug of choice for gonorrhea, and also used extensively for infections caused by Enterobacter, Serratia, Haemophilus influenza and other bacteria. Ceftriaxone is readily soluble in water (ca 40g/10ml at 25°C) but it is not orally active due to its instability to acid.

The present invention can also be used to provide a stable, solid-phase vehicle for delivery of lipoxygenase inhibitors, water insoluble compounds that inhibit arachidonic acid from being converted into various leukotrienes. Leukotrienes are possible mediators for asthma, allergic reactions, pain, and others. These

compounds are usually oil soluble and inadequate bioavailability prevents oral administration. A glass of the present invention allows for delivery of lipoxygenase inhibitors readily into a patient's system.

A glass of the present invention can also be used to deliver ACAT inhibitors (acyl transferase inhibitors) such as Belfosdil. ACAT inhibitors are a new class of compounds that inhibit cholesterol absorption from the gastrointestinal tract. They are usually oil soluble, but a glass of the present invention allows oral delivery in solid form.

An example of how the present invention can be used to mask unpleasant tasting material is the use of a glass of the present invention containing acetaminophen. Acetaminophen is an antipyretic and analgesic with a documented bitter taste. Its solubility is 1g/70ml water, but its bitter taste is an obstacle to oral administration. A glass made according to the present invention, incorporating acetaminophen masks this bitterness.

Glasses of the present invention are also useful to increase absorption of various pharmaceuticals, including, for example, beta-blockers such as labetalol and trandate. Labetalol is a nonselective alpha and beta blocker that is used for hypertension and angina pectoris. It is water soluble (about 20 mg/ml) and is usually administered

orally, however, its oral bioavailability is only about 25%, due to its extensive first pass metabolism.

Similarly, glasses of the present invention are useful for increasing absorption of chemotherapeutic agents, such as 5FU (5-Fluorouracil). 5FU is a chemotherapeutic agent that acts as an antimetabolite. It is the antineoplast of choice in the treatment of colorectal cancer and in combination with other drugs, it provides chemotherapy of first choice in the treatment of breast cancer, squamous cell carcinoma of the head and neck, non-small cell carcinoma of the lung, testicular and prostatic carcinomas, and others. It is administered intravenously and topically. Oral administration is desirable but presently not possible due to high first pass elimination. Its water solubility is 1g/80ml water, with the solubility in aqueous solutions increasing with increasing pH.

Glasses of the present invention are useful for administering drugs having toxicity, such as Methotrexate and Mechlorethamine HCl. Methotrexate (MTX) is a chemotherapeutic agent that acts as an antimetabolite. It is the antineoplastic of choice for CNS prophylaxis in acute lymphocytic leukemia. It is a component of the first-choice combination for induction and maintenance in acute lymphocytic leukemia, cervical cancer, breast cancer, non-Hodgkin's lymphomas and Burkitt's lymphoma. Mechlorethamine HCl is an alkylating agent called a

nitrogen mustard. It is used in combinations known as MOPP (mechlorethamine, vincristine, procarbazine, prednisone) and MOP (MOPP without prednisone) - two first choice treatment for Hodgkin's disease. It is very soluble in water, but high toxicity have limited its use and also limited its administration to the intravenous acute.

Glasses of the present invention when used as drug delivery agents can be administered to humans or animals in a variety of forms, including dry powder form, encapsulated, compressed into tablet form, solid foam form, and emulsion form.

Another use of the present invention is in the area of blood substitutes. Fluorodecalins have been used in connection with blood substitutes, including perfluorodecalins, however, they are problematic in that they form unstable emulsions requiring high levels of surfactants. Emulsions of the present invention using perfluorodecalin are more stable and are formed without the use of a surfactant. The multiple emulsions made according to the present invention are effective at solubilizing hemoglobin, thus providing new blood substitutes.

In numerous applications, including enzyme reactions, and toxic and hazardous waste clean-up, separation of phases presents a problem. Most often, separation is performed on

successive batches. Emulsions of the present invention are useful as continuous extraction agents.

For example, in enzyme reactions, the emulsions of the present invention help to separate enzymes or cells from waste products or cell products continuously. Emulsions of the present invention are useful in continuous extraction systems to separate heavy metals, e.g., by the creation of a gradient to pull heavy metals into the interior phase of the emulsion. Such systems may utilize, for example, proton shift or chelate technology in the interior phase. A related use of the glasses of the present invention is in the area of enzyme immobilization.

EXAMPLES

Example 1: Production of PVP-Mineral Oil Self-Emulsifying Glasses

Heavy mineral oil (USP, 0.25 g) was mixed with 1.0 g of linear PVP (with a molecular weight of about 30,000) in a beaker. Analytical grade methanol was added in a volume sufficient to dissolve all the PVP. The methanol was then evaporated from the PVP-oil-methanol mixture by rotoevaporation on a Buchi rotoevaporator with a vertical condenser. A stir bar in the rotoevaporation flask provided additional agitation during rotoevaporation. A flaky solid was obtained. When about 2 ml of doubly distilled water was added to about 200 mg of the solid, a oil-in-water emulsion was formed.

Example 2: Preparation of Sucrose-Mineral Oil Self-Emulsifying Glasses

Sucrose (2.2 g) was mixed with a volume of doubly distilled water sufficient to dissolve it. Heavy mineral oil (USP, 0.5 g) was then added to this solution. The mixture was rotoevaporated with application of mild heating (i.e., at temperatures less about 50°C). The resulting solid had a fluffy appearance. When about 2 ml of doubly distilled water was added to about 200 mg of the solid, an oil-in-water emulsion was readily formed.

The oil-in-water emulsion incorporating sucrose was found to have little or no detectable sweet-taste in a qualitative taste test.

Example 3: Preparation of Sucrose-Olive Oil Self-Emulsifying Glasses

Sucrose (2.0 g) was mixed with 0.5 g of olive oil and a volume of doubly distilled water sufficient to dissolve the sucrose. The resulting mixture was rotoevaporated until dry giving a clear film which lined the flask. A sufficient amount of doubly distilled water was added to the film-lined flask to result in oil-in-water emulsion.

The minimum amount of an aqueous phase required to be added to a particular self-emulsifying glass in order to form an oil-in-water emulsion can be readily determined by qualitative visual inspection or by more quantitative measurement. As is well-known in the art an oil-in-water emulsion, in which the external phase is water or an aqueous solution, will have certain bulk properties like that of an external aqueous phase, for example, the emulsion will not visually appear oily or feel oily to the touch. A more quantitative assay of whether or not water is the external phase involves addition of a small amount of a water-soluble dye to the emulsion. If the colored dye

disperses in the external phase (i.e., the emulsion becomes colored) it is an aqueous phase.

The actual amount above the minimum of an aqueous phase that is added to form an oil-in-water emulsion depends on the desired application of the emulsion.

Example 4: Preparation of Carboxymethylcellulose-Mineral Oil Self-Emulsifying Glasses

Carboxymethylcellulose (Aqualon, Wilmington, Delaware) and heavy mineral oil (USP) were combined in a 4:1 weight ratio. A volume of doubly distilled water sufficient to dissolve the carboxymethylcellulose was then added. The combination was rotoevaporated to dryness. Addition of about 10 ml of doubly distilled water to the film resulted in the formation of a viscous oil-in-water emulsion.

Example 5: Preparation of Sucrose-Safflower Oil Self-Emulsifying Glasses Containing Progesterone

Progesterone (0.5 g) was dissolved in 0.5 g safflower oil. Sucrose (2.0 g) was combined with the progesterone-oil solution. Doubly distilled water was then added in an amount sufficient to dissolve the sucrose. The resulting combination was rotoevaporated in a flask containing a stir bar until dry. The resulting solid, when combined with water, formed a oil-in-water emulsion having progesterone in the oil phase.

A similar preparation was made using mineral oil in place of safflower oil. The progesterone was observed to be more soluble in safflower oil than in mineral oil.

Example 6: Preparation of PVP-Mineral Oil Self-Emulsifying Glass, Chloroform Method

Linear PVP (molecular weight about 30,000) and heavy mineral oil (USP) were combined in a 4:1 weight ratio. An amount of chloroform sufficient to dissolve both the oil and the PVP was added. The resulting solution was left to stand at room temperature to allow the solvent to evaporate giving a dry solid. Doubly distilled water was added to the dry solid and a oil-in-water emulsion was formed. A similar dry solid material can be prepared by removal of the solvent by rotoevaporation.

Example 7: Preparation of Synthetic Sweetener - Mineral Oil Self-Emulsifying Glasses.

Sodium cyclamate was combined with mineral oil in the weight ratio of 3.5:1. An amount of doubly distilled water sufficient to dissolve the sodium cyclamate was then added to the combination. Water was removed from the combination by rotoevaporation. A glass solid resulted. Addition of water to this solid resulted in the formation of an oil-in-water emulsion.

Soluble saccharin, i.e., sodium saccharin dihydrate, was combined with mineral oil in the weight ratio of 3.5:1, and a sufficient amount of water to dissolve the saccharin emulsifying glass was prepared by removal of water from the combination via rotoevaporation. Addition of water to the resulting glass solid produced an oil-in-water emulsion.

The cyclamate and saccharin-based emulsions were found to retain a sweet taste by qualitative direct tasting of the

emulsions. The emulsions were significantly less sweet-tasting, however, than equivalent amounts of the sweeteners themselves.

Example 8: Preparation of Stable Oil-in-Water Emulsions with 95% Aqueous Ethanol, 1 N HCl and 1 N NaOH

A self-emulsifying glass was prepared by rotoevaporating a mixture of sucrose, heavy mineral oil (USP) and doubly distilled water; the weight ratio of sucrose to mineral oil in the mixture and the result and glass was 4:1.

Between about 100 mg and about 200 mg of the solid was mixed with between about 1 and about 2 ml of each of the following: 95% aqueous ethanol, 1 N HCl and 1 N NaOH. In each case, a stable oil-in-water emulsion was formed.

The 95% ethanol, NaOH and HCl sucrose-mineral oil emulsions were stored in sealed containers at room temperature for one week. No phase separation was observed in any of these emulsions during that time.

An attempt to prepare a similar emulsion by adding absolute ethanol to the self-emulsifying glass solid resulted in no emulsion formation. The glass did not dissolve nor appear to hydrate in the absolute ethanol. The glass remained at the bottom of the container. No oil release was observed.

These results indicate that the emulsions formed from the self-emulsifying glasses of the subject invention are surprisingly stable under conditions that usually crack surfactant-containing emulsions (addition of alcohol, extremes of pH). Further, although significant variations in water content of the aqueous phase can be tolerated without compromising emulsion formation, it appears that

there must be at least a small percentage of water in the aqueous phase to assure emulsion formation.

Example 9: Effect of Repeated Freeze-Thawing Cycles on Emulsion Stability

Sucrose and castor oil were combined in a 2:1 weight ratio. An amount of doubly distilled water sufficient to dissolve the sucrose was added. The resulting mixture was rotoevaporated to produce a dry non-oily solid. About 200 mg of the dry solid glass was added to about 2 ml of doubly distilled water to form an oil-in-water emulsion. Thereafter, the emulsion was successively frozen at about -7°C and thawed at about 25°C at least 40 times. The emulsion was not cracked by this treatment. After each freeze-thaw cycle, the light scattering, a function of the particle size of the emulsion, was indirectly determined using a Baush and Lomb Spectrophotometer 100. The repeated freeze-thaw cycles did not affect the particle size of the emulsion.

Example 10: Stability of a Sucrose-Mineral Oil Emulsion

A self-emulsifying glass was prepared as described above in Example 2, with sucrose and mineral oil in the ratio of 6:1. Distilled water or normal saline were added to the glass to produce oil-in-water emulsions. In addition, a physical mixture of oil, sucrose and water (in the same weight ratios as in the emulsions prepared from the glasses) was subjected to emulsive mixing, i.e., vigorous vortexing, for 20 minutes to produce a dispersion. The turbidity (at 400 nm) of the two emulsions and the dispersion were compared as a function of time (up to about 22 hrs). Each transmission measurement was corrected for drift with a reference tube containing 3 ml of doubly distilled water. The turbidity of the sample provides a measure of the particle size of an emulsion. Furthermore,

the turbidity of a sample will decrease on cracking of an emulsion or disruption of a dispersion. A change in particle size is distinguished from emulsion cracking as emulsion cracking is accompanied by visual phase separation.

The results of the turbidity measurements on the emulsions and dispersions containing mineral oil and sucrose are given in Figure 1. The emulsions prepared from glasses were found to be considerably more stable than the dispersion in which decreased turbidity accompanied by visual signs of phase separation was observed in 5-10 minutes. The water-based emulsion displayed constant turbidity for 4-5 hrs after which turbidity slowly decreased with time. The normal saline emulsion, in contrast, displayed a more rapid decrease in turbidity with time after about 10 minutes. In contrast to the dispersion, however, the emulsions did not crack with decreasing turbidity. No visible phase separation was detected over the course of the experiment. The significant decreases in turbidity observed are believed to be the result of decreasing particle size in the emulsion with time. This effect is more pronounced at shorter times (at least in rate) when normal saline is employed as the aqueous phase.

Example 11: Stability of a PVP:Mineral Oil Emulsion

Heavy mineral oil (USP) and linear PVP (molecular weight about 30,000) were mixed in a weight ratio of 1:5. An amount of analytical grade methanol sufficient to dissolve the PVP was added to the combined oil and PVP. The resulting mixture was rotoevaporated to remove methanol. The resulting solid (100 mg) was combined with about 3 ml doubly distilled water to form an oil-in-water emulsion.

For comparison to the above described emulsion, dispersions of heavy mineral oil (USP) and linear PVP (weight ratio of 1:5) in distilled water (same amount as used in the emulsion) were prepared either by passage of the combined ingredients through a colloid mill (under temperature control) or by vortexing until a maximum turbidity was obtained (as assessed by visual observation). These dispersions contained no emulsifier and were an appropriate comparison for the non-emulsifier based oil/PVP emulsion.

The turbidity (% Transmission at 400 nm) of the emulsion and the two dispersions produced as described were measured as a function of time up to about 22 hours as described in Example 10, and the systems were visually observed for any physical changes, e.g., phase separation. The emulsion formed from the PVP:oil self-emulsifying glass was considerably more stable than either of the dispersions prepared. In both the vortexed and the colloid mill-prepared dispersion a rapid phase separation was observed within at most 5 min. The emulsion was, in contrast, found to be stable to phase separation for at least about 20 hours.

A very slow decrease in turbidity was observed at times over about 7 hours in the PVP:oil based emulsions. This decrease in turbidity was not accompanied by a visual phase separation and thus did not signal cracking of the emulsion. Slowly over the course of a number of days the emulsion became visually clear, apparently as a result of decreasing particle size in the emulsion.

Example 12: Conductivity of Sucrose-Mineral Oil Emulsions

Aliquots of doubly distilled water were incrementally added to 0.4615 g of the self-emulsifying glass prepared as described in Example 2; conductivity of the resulting sample was measured after each addition. Conductivity is derived from resistance measurements made with a Fluke 73 multimeter. The data are summarized in Figure 2 in which the conductivity of the sample is shown relative to that of water at 25°C.

The conductivity results with the emulsions formed from self-emulsifying glass have unique patterns compared to similar measurements of standard emulsions containing known emulsifiers.

In Figure 2, conductivity is observed to increase as a function of the weight fraction of water. A region of fluctuating conductivity is observed in the results of Figure 2, hatched area (about 90% to 96% water). In this region, conductivity of the sample fluctuates between conducting and non-conducting. It is unclear what is the origin of such fluctuating conductivities in the emulsions of the present invention. The fluctuations are not observed to be associated with the transition between a water-in-oil emulsion and an oil-in-water emulsion. The exact range of water weight fraction over which the fluctuation is observed has been found to vary with relative amounts of matrix compound and oil in the self-emulsifying glass. In several instances, multiple regions of fluctuation have been detected as a function of water weight fraction. Although the conductivity fluctuation phenomena in these emulsions have not been fully characterized, it is hypothesized that these regions of fluctuation may be associated with the presence of liquid crystalline phases in the emulsions of the present invention. In any event, the presence of relatively broad

regions of conductivity fluctuation and the presence in some instances of multiple regions of such fluctuations are believed to be characteristic of emulsions formed from self-emulsifying glasses.

Discontinuities in conductivity has been observed with microemulsions which have been associated with a percolation transition (Legues and Sauterey (1980) Phys. Chem. 84:3503). Percolation in microemulsions is reported to be dependent on persistence lengths and interfacial rigidities (de Gennes and Taupin (1982) J. Phys. Chem. 86:2294; Lam et al. (1987) J. Colloid Interface Sci. 120:30; and Guest et al. (1985) J. Physique Lett. 46:L-1055).

In contrast, the conversion of a conventional emulsion containing a emulsifier from a water in oil to an oil in water emulsion has been reported to be abrupt, as manifested by a rapid shift in conductivity. (K. Shinoda, H. Arai (1967) J. Colloid Interface Sci. 25:429).

The relative conductivity of the emulsions of the present invention above the "fluctuating" region is greater than 1, i.e., the continuous phase has a conductivity greater than that of bulk water. It is believed that this is due to an imposition of an order or structure on the water external phase by the emulsion particles at higher water content, possibly via the formation of liquid crystals, whereby the water phase more readily conducts current. The lower conductivities below the fluctuating region is associated with a more complex structure and less entropy.

Example 13: Effect of Shear Stress on Emulsion Structure as Measured by Viscosity

An oil-in-water emulsion was formed by adding 1 ml of doubly distilled water to 552.4 mg of the sucrose-mineral oil solid prepared as described in Example 2. The resulting emulsion was stirred at about 60 rpm (for about 1 hour) until a minimal viscosity reading was obtained. The viscosity of the emulsion was then periodically measured with minimal input of additional shear stress. Viscosity was measured with a Brookfield cone/plate viscometer whose spindle was set at the minimum value of 0.3 rpm. The spindle was turned only long enough to obtain a viscosity measurement. The results are presented in Table I:

Table I

Time (hours)	Viscosity (cps)
0	40.1[1]
3	58.1
4	76.2
6	84.1
21	114.0
27	134.0

[1]Lowest cps achieved after approximately 1 hour of stirring. All other cps values were measured immediately after turning on the spindle.

The purpose of this experiment was to determine if the structure of the emulsion formed during the preparations as described herein, would be reformed after disruption by application of shear stress (60 rpm stirring). As can be seen by the data in Table II, the emulsion slowly increased in viscosity with time indicating that the disrupted

structure was slowly reformed. If it is assumed that the emulsion structure comprises an oil core encased in a shell of sucrose molecules with water molecules hydrogen bonding to hydroxyl groups, the results of Table II can be explained as follows: The emulsion particles lost hydration during the initial shearing interval, thus decreasing viscosity. A hydrated structure was reformed in the emulsion and viscosity increased over time. The ability of the emulsion particles to regain a structure disrupted by application of shear stress rationalize the observed stability of the emulsion and its resistance to cracking by shear stress.

Example 14: Viscosity of Sucrose-Mineral Oil Emulsion as a Function of Temperature

The viscosities of a sucrose-mineral oil emulsion prepared as in Example 2, as a function of temperature were compared to those of control sucrose solutions. The emulsion was prepared by adding 1 ml of doubly distilled water to 0.5224 g of the glass produced in Example 2. A sucrose solution was prepared by dissolving an amount of sucrose equivalent to that amount present in 0.5524 g of the glass (0.450 g) in 1 ml water. Viscosity measurements were then made for both samples as the temperature was lowered from 40°C to 5°C. All viscosity measurements were made with a Brookfield cone/plate viscometer with a spindle speed of 60 rpm. The results are presented in Table II:

Table II

Sucrose-Mineral Oil Emulsion		Control Sucrose Solution
°C	CPS·°C	CPS
40.0	2.40	39.5 2.14
37.0	2.56	35.5 2.02
34.0	2.94	29.5 2.40
29.5	3.54	24.5 2.86
28.0	3.84	19.0 3.34
24.0	4.74	14.5 3.87
20.0	5.61	10.0 4.68
15.0	6.78	4.5 6.41
10.5	8.18	
6.5	10.2	
5.5	11.0	

The results of Table II indicate that the viscosity of the emulsion increases more rapidly with decreasing temperature than that of the sucrose solution. The increasing viscosity of the sucrose-mineral oil emulsion as a function of decreasing temperature relative to that of the sucrose solutions indicates a structure for the emulsion that is more complex than that for a sucrose solution. The data is consistent with the theory that, as the emulsion cools, it acquires additional degrees of hydration.

Example 15: Viscosity of a Water-in-Oil Emulsion as a Function of Shear Rate

The viscosity of an oil-in-water emulsion prepared from a self-emulsifying glass having a sucrose to mineral oil ratio of 6:1 was determined as a function of the shear rate at 25 ± 0.2°C. The results of this study are given in Figure 3. At low shear rates (0.3 rpm) the viscosity was high (30 cps in Figure 3) and decreased as the shear rate was increased. No macromolecules are present in these sucrose-based emulsions. It is, thus, unexpected to

observe such thixotropic behavior. The observation of thixotropic behavior can be rationalized as the result of ordered structures such as might be associated with the formation of liquid crystals in the emulsion.

Example 16: Particle Size of PVP-Mineral Oil Emulsion

Heavy mineral oil (USP, 0.25 g) was mixed with 1.25 g of linear PVP (molecular weight about 30,000) and about 200 ml of analytical grade methanol. This mixture was then rotoevaporated until dry. An emulsion was generated by the addition of water to several milligrams of the resulting solid. The particle size of the emulsion was determined by a Hiac/Royco particle size analyzer to be between about 0.5 and about 5.0 μm, with the size averaging about 4 μm.

Example 17: Rate of Formation of a PVP-Mineral Oil Emulsion

To determine the rate of emulsion formation from the solid of Example 16, doubly distilled water (3 ml) was added at time zero to a sample of the solid (127.5 mg) without mixing and the turbidity of the sample was measured. The absorbance of the samples was measured periodically. Table III summarizes the results.

Table III

Time (min)	Absorbance (400 nm)
0	0.005
0.5	0.017
2.5	0.052
50.1	12
90.5	85
280.5	73
3600.5	73

An absorbance plateau over time indicates that emulsion formation is complete. These data indicate that an emulsion is formed without mixing of ingredients.

The data also indicate that a wavelength of 400 nm does produce a Tyndall effect with these emulsion particles. Thus, at least some of the particle sizes in the emulsion must be greater than 400 nm (0.4 μm). The emulsions had a cloudy appearance, indicating the presence of particles having a diameter greater than 0.05 μm (the lower limit of visibility with the naked eye).

After the measurements noted above, the sample was stored at room temperature for 2 weeks. After this time, it was observed that the samples had become transparent even though the emulsion had not undergone phase separation. This further suggested that particle size of the emulsions had decreased over time, to form a emulsion with a particle size less than about 0.05 μm.

Example 18: X-Ray Diffraction of Sucrose-Mineral Oil Mixture and Processed Sucrose-Mineral Oil Solid

The X-ray diffractograms of a sucrose-mineral oil solid produced by the method of the subject invention and of a simple mixture of sucrose and mineral oil were obtained.

Each sample contained sucrose and heavy mineral oil (USP) in a weight ratio of 3.5:1. In sample 1, the oil and sugar were manually mixed. In sample 2, a quantity of doubly distilled water sufficient to dissolve the sucrose was added, and the water was then removed by rotoevaporation, as described hereinabove, to produce the self-emulsifying solid. Each sample was then packed into a 1 X 3 cm sample holder and run on a Scintag/USA Powder X-ray Diffractometer, Cukα, wavelength 1.54 Å, and scan

rate of 3 °C/minute. The diffractograms for each sample are presented in Figure 4.

The diffractograms indicate that the sucrose in the simple mixture retains its crystalline structure, as expected. In contrast, the processed sucrose and mineral oil glass appears amorphous by this experimental technique. The X-ray diffraction technique can detect more than about 10% long range molecular order from crystal formation.

Diffractograms of sucrose-mineral oil solid emulsions having sugar to oil weight ratios of 2.5:1 and 4:1 were also measured. These self-emulsifying solids also appear to be amorphous by X-ray diffraction.

Example 19: Use of Sucrose-Mineral Oil Emulsion for Dispersion and Recovery of Oil

To about 200 mg of the sucrose-mineral oil solid emulsion of Example 2 was added about 2 ml of doubly distilled water to form the emulsion. An additional 2 ml of heavy mineral oil (USP) was subsequently added to the emulsion. The additional oil was observed to readily disperse in the system; there was no evidence of phase separation. The dispersion took place without the addition of work (e.g., stirring) to the system. This example indicates that oil need not go through the method the subject invention in order for it to be integrated into the emulsion particles.

Example 20: Preparation of Sucrose-O/W Emulsion-Containing Self-Emulsifying Glass

A primary emulsion was prepared by emulsifying an aqueous solution with heavy mineral oil to which a lipid soluble surfactant: Arlacel-C, Span 80 or Span 85 (Trademarks ICI Americas Inc., USA) had been added. The surfactant was added to the oil and the mixture was

homogenized using a Brinkman Homogenizer (Sybron Corporation, USA) with a small impeller attachment for 40-60 seconds. The aqueous phase was then slowly added. After addition was complete, homogenization was continued until the desired water-in-oil emulsion was obtained. Emulsions having 70%-79% wt/wt heavy mineral oil, 5.5%-7.2% wt/wt surfactant (HLB 1.8-4.3) and 21%-30% of an aqueous phase were prepared.

Sucrose was combined with the primary W/O emulsion in the weight ratio about 78:22. Doubly distilled water was then added to dissolve the sucrose. The combination was subjected to rotoevaporation (at about 5 mmHg). The flask containing the combination was rotated at about 17-25 rpm on the rotoevaporator and the temperature of the flask was maintained at about 32°C. Water was removed from the combination until a dry "foam-like" material was produced. The solid was collected as a powder and stored in a desiccator at room temperature. It has been found that the solid self-emulsifying glass can be stored in this way for relatively long times (weeks or months) without loss of its self-emulsifying property.

Addition of an aqueous phase to the solid results in formation of multiple W/O/W emulsion. For example, addition of 5 ml of water, 1 N HCl, or 1 N NaOH to 1 g of solid results in the formation of a stable multiple emulsion. In contrast, the solid is not dispersed in heavy mineral oil; the solid settles to the bottom of the container of mineral oil, since the density of the glass solid is greater than that of oil. This result is consistent with the solid containing internal droplets of water or aqueous phase (of the primary emulsion).

The glass was analyzed using differential scanning calorimetry using methods conventional in the art such as those described in Ford and Timmins (1989) Pharmaceutical

Thermal Analysis Ellis Horwood Ltd., England, which is incorporated in its entirety by reference herein, see Figure 5, thermogram A. The glass transition of the glass was found to be approximately 57°C with recrystallization of sucrose observed at approximately 120°C and finally at approximately 185°C any crystalline sucrose in the glass melts.

DSC analysis was performed on the self-emulsifying glasses produced using sucrose and mineral oil. The DSC thermograms of the sucrose-mineral oil glasses are analogous to that of the sucrose/primary emulsion glass thermogram of Figure 5, thermogram A, in that a glass transition, sucrose recrystallization and sucrose melting feature are observed. The relative size of the peak associated with the melting of crystalline sucrose will vary dependent on the amount of microcrystallinity in the glass. DSC measurement can in fact be readily employed to determine the amount of microcrystallinity in a particular glass sample. The glass transition temperature may vary dependent on the exact composition of the glass.

A DSC thermogram of a physical mixture of sucrose and mineral oil exhibits no glass transition. The thermogram contains only a feature associated with the melting of crystalline sucrose at about 185°C.

Example 21: Preparation of a Self-Emulsifying Glass containing Sucrose-Maltodextrin and a W/O Emulsion

A primary emulsion was prepared as described in example 21. A mixture of sucrose containing 3% (wt/wt) maltodextrin was added to the emulsion in the weight ratio of about 78:22 and sufficient water was added to dissolve the sucrose/maltodextrin. Removal of the water by rotoevaporation resulted in a dry solid which was found to

form a W/O/W emulsion on contact with an aqueous phase. For example, addition of 5 ml of water, 1 N HCl, or 1 N NaOH to 1 g of solid results in the formation of a stable multiple emulsion.

The glass was analyzed using differential scanning calorimetry, see Figure 5B. The glass transition temperature of this glass is raised significantly compared to the sucrose containing glass of the example 21 (to greater than about 180°C). No sucrose recrystallization is detected and any crystalline sucrose in the glass is observed to melt. Addition of maltodextrin to the sucrose carrier results in much higher glass transition temperatures than with sucrose alone. Higher glass transition temperatures are likely to be associated with increased stability of the self-emulsifying systems in the solid state and to result in longer shelf-life of these glasses and products based on these glasses.

Example 22: Structure of the Multiple Emulsions

Water soluble and/or lipid soluble dyes were incorporated into self-emulsifying glasses in order to examine the structure of the emulsions that were formed from these glasses.

Primary emulsions were prepared as described in Example 20 with heavy mineral oil and surfactant. The lipid soluble dye D&C violet 2 was added to the oil phase and the water soluble dye FD&C red 17 was added to the internal aqueous phase. A sucrose/primary emulsion glass containing both dyes was prepared and water was added to that glass to form a W/O/W emulsion. The emulsion was then examined under a microscope (400 power magnification) and was found to contain a visually red internal phase and a blue-grey oil phase. Three types of W/O/W emulsion droplets were observed in emulsions: droplets having a small outer

droplet surrounding one large inner droplet (Type A), droplets composed of larger exterior phases containing smaller, multiple interior droplets (Type B) and droplets having an even larger exterior oil phase containing small aqueous droplets too numerous to count (Type C). Type A, B and C droplets have been described previously in multiple emulsions (see Florence and Whitehill (1981)). The sucrose-based multiple emulsions examined were composed of approximately 80% Type A droplets. The remainder being either type B or C droplets.

The particle size of these sucrose-based W/O/W emulsions was determined as a function of time after emulsion preparation. Particle size measurement were taken at preparation, at 7 days after preparation and at 30 days after preparation. The average diameters for the outer and inner membrane of the emulsion droplets were 12.4 micron and 3.9 micron, respectively immediately after emulsion preparation. These diameters did not significantly change at 7 and 30 days after preparation. The emulsions were also visually inspected under the microscope at 60 and 90 days after preparation and were found to remain intact.

Example 23: Production of Matrix Compound - W/O Emulsion-Containing Self-Emulsifying Glasses.

The following general procedures can be employed with any water-soluble non-surface active matrix compound (polymer or non-polymer) of the present invention, and with any water-in-oil emulsion including, among others, sucrose, fructose, trehalose, cyclamate, saccharine and the water-soluble polymers PVP cellulose derivatives and maltodextrin.

A primary water-in-oil emulsion is formed by conventional art-known techniques employing a lipid soluble surfactant. Surfactants appropriate for the formation of water-in-oil

emulsions are employed, specifically those having HLB values less than about 5. Anionic, cationic or non-ionic surfactants can be employed. An aqueous phase is combined with an oleaginous material and the surfactant and the primary W/O emulsion is formed by vigorous mixing (i.e., emulsive mixing).

Once the primary emulsion is produced, it is combined with the desired matrix compound and an amount of an aqueous solution sufficient to dissolve the matrix compound. Water is then removed from the resulting combination to give a solid, foam or film which appears to be dry. The dry-appearing solid is found to be a self-emulsifying glass. Addition of a sufficient amount of an aqueous phase to the glass results in the formation of a stable multiple emulsion, i.e., a W/O/W emulsion. Table IV provides a representative list of preparations of self-emulsifying glasses containing a water-in-oil emulsion. Various vegetable and hydrocarbon oils were employed in these examples, specifically, corn, peanut, olive, safflower, soybean, castor and mineral oils. No significant differences were observed among these oils. The phase ratios (v/v) of oil: aqueous phase in the primary emulsions employed, ranged from about 4:1 to 2:1. In the exemplified glasses, non-ionic surfactants having the indicated HLB value were used, for example, Arlacel C (Trademark). Specifically exemplified matrix compounds are sucrose, PVP and mixtures of sucrose and maltodextrin. The weight ratio of matrix to emulsion specifically exemplified, ranged from about 1:1 to 9:1. (Representing matrix to oil weight ratios ranging from about 1.2:1 to about 10:1.)

Each of the combinations listed in Table IV resulted in a self-emulsifying glass which, on addition of an aqueous phase, resulted in formation of a multiple emulsion. In several of the exemplified systems an active ingredient was

incorporated into the aqueous phase of the primary emulsion. The aqueous phase of the primary water-in-oil emulsion becomes the internal aqueous water-in-oil phase (i.e., the second aqueous phase) of the W/O/W emulsion. Water soluble active ingredients such as dyes and pharmaceutical agents are exemplified. The aqueous phases of the primary emulsion can range in pH from 10 to 1 and may include inorganic salts. The oil phase of the primary emulsion can also contain an active ingredient, usually lipid soluble.

Example 24: W/O/W Emulsions Containing Canrenoic Acid

Primary emulsions were prepared by emulsifying an aqueous solution with heavy mineral oil to which the surfactant Arlacel-C (HLB 3.7, Trademark ICI Americas Inc., USA) had been added. The aqueous phase was prepared to be either 0.0614 M or 0.439 M in canrenoic acid K^+ salt. The surfactant was added to the oil and the mixture was homogenized using a Brinkman Homogenizer (Sybron Corporation, USA) with a small impeller attachment for 40-60 seconds. The aqueous phase was then slowly added to the oil phase. After addition was complete, homogenization was continued until the desired water-in-oil emulsion was obtained. The primary emulsions contained about 71.4% mineral oil, about 21.4% aqueous phase and about 7.1% surfactant. Sucrose was combined with the primary W/O emulsion in the weight ratio about 78:22. Doubly distilled water was then added to dissolve the sucrose. The combination was subjected to rotoevaporation to produce a dry "foam-like" solid. Addition of water to the solid resulted in a W/O/W emulsion. Examination of the external water phase of the multiple emulsion employing infrared spectroscopy immediately after preparation of the emulsion detected no canrenoic acid in the external phase. Canrenoic acid was slowly released from the internal phase of the multiple emulsion as a function of time. Multiple

emulsions such as that exemplified can function as slow release drug delivery systems.

Example 25: Preparation of O/W Emulsion I

A lipoxygenase inhibitor is dissolved in olive oil in a flask to make a concentrated solution. PVP is added in the ratio of 8:4:1::PVP:Oil solution. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another aqueous phase is added to the solid, a stable O/W emulsion results.

Example 26: Preparation of O/W Emulsion II

A lipoxygenase inhibitor is dissolved in olive oil in a flask to make a concentrated solution. PVP is added in the ratio of 8.4:1::PVP:Oil solution. Chloroform is added until the PVP dissolves. The chloroform is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another aqueous phase is added to the solid, a stable O/W emulsion results.

Example 27: Preparation of O/W Emulsion III

An ACAT inhibitor is dissolved in corn oil in a flask to make a concentrated solution. PVP is added in the ratio of 3.5:1::PVP:Oil solution. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another aqueous phase is again added to the solid, a stable O/W emulsion results.

Example 28: Application of a O/W Emulsion to Blood Substitutes

Perfluorodecalin, an oil capable of solubilizing oxygen, is thoroughly gassed with carbon dioxide on ice. It is then mixed with PVP (22% perfluorodecalin, 78% PVP) in a flask. Cold water is added until the PVP dissolves, leaving a two-phase system. The water is then removed in a rotoevaporator, leaving a foamy solid. An aqueous solution consisting of a physiological salt solution containing NaCl (0.6%), MgCl2 (0.02%), KCl (0.03%), sodium lactate (0.31%), glucose (0.1%) is added, forming a stable O/W emulsion. The resulting oil-in-water emulsion can be employed in a blood substitute composition.

Example 29: Preparation of W/O/W Emulsion I

A primary emulsion of 70% vegetable oil, 7% Arlacel C and 23% aqueous solution containing insulin, glycerin and m-cresol (2.5 mg/ml) is prepared in an agitator. It is mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another aqueous phase is added to the solid foamy material, a stable W/O/W emulsion results.

Example 30: Preparation of W/O/W Emulsion II

A primary emulsion of 70% soybean oil, 7% Arlacel C and 23% aqueous solution containing 40% ceftriaxone at pH 6.7 is prepared in a homogenizer. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another

aqueous phase is added to the solid, a stable W/O/W emulsion results.

Example 31: Preparation of W/O/W Emulsion III

A primary emulsion of 70% heavy mineral oil, 7% Arlacel C and 23% aqueous solution containing 1.5% acetaminophen and is prepared in an agitator. It is mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion in a flask. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another aqueous phase is added again to the solid, a stable W/O/W emulsion results.

Example 32: Preparation of W/O/W Emulsion IV

A primary emulsion of 70% peanut oil, 7% Arlacel C and 23% aqueous solution containing 20 mg/ml labetalol in water at pH 2-4 is prepared in a homogenizer. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water is added again, a stable W/O/W emulsion results.

Example 33: Preparation of W/O/W Emulsion V

A primary emulsion of 70% mineral oil, 7% Arlacel C and 23% aqueous solution containing 1.25% 5-fluorouracil (5FU) at pH 8.0 is prepared in a homogenizer. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another aqueous phase is added again to the solid, a stable W/O/W emulsion results.

Example 34: Preparation of W/O/W Emulsion VI

A primary emulsion of 70% safflower oil, 7% Arlacel C and 23% aqueous solution containing 1 mg/ml Methotrexate (2% bovine serum albumin) is prepared in a homogenizer. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another aqueous phase is added again to the solid, a stable W/O/W emulsion results.

Example 35: Preparation of W/O/W Emulsion VII

A primary emulsion of 70% light mineral oil, 7% Arlacel C and 23% aqueous solution containing 2 mg/ml mechlorethamine HCl, at pH 6 is prepared in an agitator. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water or another aqueous phase is added again to the solid, a stable W/O/W emulsion results.

Example 36: Preparation of W/O/W Emulsion VIII; W/O/W Emulsion for Blood Substitutes

A primary emulsion of 70% vegetable oil, 7% Arlacel C and 23% aqueous solution (isotonic 10MM phosphate at pH 7.1, 1% Hemoglobin) is prepared in an agitator. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Cold water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. An aqueous solution containing NaCl (0.6%), MgCl2 (0.02%), KCl (0.03%), sodium lactate (0.31%), and glucose (0.2%) is

added, forming a stable W/O/W emulsion. The exemplified water-in-oil-in-water emulsion ca be employed in a blood substitute.

Example 37: Preparation of W/O/W Emulsion IX

A primary emulsion of 70% light mineral oil, 7% Arlacel C and 23% of 0.06% urease solution in water is prepared in an agitator. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water is added again, a stable W/O/W emulsion results.

Example 38: Preparation of W/O/W Emulsion X

A primary emulsion of 70% light mineral oil, 7% Arlacel C and 23% aqueous solution consisting of 5 mg/ml LH-RH analog in NaCl for tonicity and 9 mg/ml of benzoyl alcohol is prepared in a homogenizer. It is then mixed in a flask with sucrose in the ratio of 3.5:1::sucrose:primary emulsion. Water is added until the sucrose dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water is added again, a stable W/O/W emulsion results.

Example 39: Preparation of W/O/W Emulsion XI

A primary emulsion of 70% light mineral oil, 7% Arlacel C and 23% of 2N sulfuric acid is prepared in an agitator. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water is added again, a stable W/O/W

emulsion results which is useful in continuous flow extraction for cationic toxic materials.

Example 40: Preparation of W/O/W Emulsion XII

A primary emulsion of 70% light mineral oil, 7% Arlacel C and 23% of aqueous phase with 10% EDTA is prepared in an agitator. It is then mixed in a flask with PVP in the ratio of 3.5:1::PVP:primary emulsion. Water is added until the PVP dissolves, leaving a two-phase system. The water is then removed using a rotoevaporator, leaving a solid, foamy material. When water is added again, a stable W/O/W emulsion results which is useful in continuous flow extraction for toxic materials that can form complexes with chelate.

Example 41: Drug Delivery using Self-Emulsifying Glasses

A self-emulsifying glass is prepared by the method of Example 2 from a mixture of sucrose and an oil suitable for pharmaceutical applications and internal administration, such as mineral oil. All preparation are done under conditions appropriate for the preparation of human pharmaceuticals. The ratio of sucrose to oil is at least about 2:1. A lipid-soluble active ingredient which has medicinal activity, i.e., a lipid-soluble drug, is dissolved in the oil phase prior to processing to form the glass. Processing conditions are such that the activity of the drug is substantially unaffected. The resultant glass incorporates the lipid-soluble active ingredient. The glass is introduced into a capsule or other similar means appropriate for administration of solid drug agents to humans or animals. The amount of glass solid in the capsule is adjusted to provide a desired dosage. The capsule may also include an appropriate filling agent. Alternatively or in addition, the concentration of active ingredient in the oil phase can be adjusted to achieve a

desired dosage range. The resultant capsule is orally administered to the human or animal patient to provide a desired dose of the medicinal agent.

A self-emulsifying glass prepared as described above to contain a lipid-soluble drug can be employed in the preparation of tablets for oral drug administration.

Example 42: Drug Delivery using Self-Emulsifying Glasses

A self-emulsifying glass is prepared by the method of Example 2 from a mixture of sucrose and an water-in-oil emulsion suitable for pharmaceutical applications and internal administration. All preparations are done under conditions appropriate for the preparation of human pharmaceuticals. The ratio of sucrose to oil in the water-in-oil emulsion is at least about 2:1. A water-soluble active ingredient which has medicinal activity, i.e., a water soluble drug, is dissolved in the aqueous phase prior to formation of the water-in-oil emulsion. Processing conditions are such that the activity of the drug is substantially unaffected. The resultant glass incorporates the water soluble active ingredient. The glass is introduced into a capsule or other similar means appropriate for administration of solid drug agents to humans or animals. The amount of glass solid in the capsule is adjusted to provide a desired dosage. The capsule may also include an appropriate filling agent. Alternatively or in addition, the concentration of active ingredient in the aqueous phase of the water-in-oil emulsion can be adjusted to achieve a desired dosage range. The resultant capsule is orally administered to the human or animal patient to provide a desired dose of the medicinal agent.

A self-emulsifying glass prepared as described above to contain a water soluble drug can be employed in the preparation of tablets for oral drug administration.

Example 43: Food Preparation using Self-Emulsifying Glasses

Sucrose is mixed with a volume of aqueous solution sufficient to dissolve it. The aqueous solution contains water-soluble ingredients suitable for food preparations, including a flavoring agent such as vanilla extract. Added to this is an oil suitable for use in food preparations, such as vegetable oil. A lipid-soluble ingredient, such as a flavoring agent, is dissolved in the oil prior to mixing with the sucrose solution. The ratio of sucrose to oil is at least about 2:1. The mixture is subjected to evaporation to remove the water, leaving a glass solid. The glass solid is mixed with other food ingredients, including flour, additional sugar, baking soda, spices, and baking powder. This mixture is then stored until needed for preparation into the final food product. When needed, the mixture is mixed with water to form a batter suitable for baking a cake or similar preparation. No egg or other emulsifying agent is needed.

All references cited in the foregoing specification and examples are incorporated in their entirety by reference herein.

Those of ordinary skill in the art of emulsion technology and drug delivery will appreciate that alternative techniques, procedures, methods and reagents other than those specifically described in the forgoing examples can be readily employed or substituted to achieve the objects, i.e., the glasses, emulsions, multiple emulsions and drug delivery agents, of the present invention. Alternative, but functionally equivalent, reagents, solvents and methods will be readily apparent to those of ordinary skill in the art and can be applied to the present invention without expense of undue experimentation. All such alternatives, variations and equivalents are to be considered to be encompassed within the spirit and scope of the present invention.

Table IV

REPRESENTATIVE SELF-EMULSIFYING GLASSES AND W/O/W EMULSIONS

Matrix Compound	% Matrix	Emulsion Contents				Active Ingredients[1]
		% Oil	% Aqueous Phase	% Surfactant	HLB Surfactant	
Sucrose	77.8	71.4	21.4	7.1	2.55	0.1N NaOH/3.33% Thymol Blue
Sucrose	77.8	72.7	21.8	5.5	1.8	0.1N NaOH/3.33% Thymol Blue
Sucrose	77.8	72.7	21.8	5.5	1.8	0.1N NaOH/0.01 gm FD&C Red #17
Sucrose	77.8	72.7	21.9	5.5	3.7	0.1N NaOH/0.01 gm FD&C Red #17
Sucrose	77.8	71.4	21.4	7.1	3.7	0.1N NaOH/0.01 gm FD&C Red #17/ 0.02 gm D&C Violet #2 in Oil
Sucrose	77.8	71.4	21.4	7.1	3.7	0.0614M Canrenoic Acid K$^+$
Sucrose	77.8	71.4	21.4	7.1	3.7	0.439M Canrenoic Acid K$^+$
PVP C-15	77.8	71.4	21.4	7.4	3.7	500μ/ml Reg. Pork Insulin
Sucrose	90.9	71.4	21.4	7.1	3.7	500μ/ml Reg. Pork Insulin
Sucrose	77.8	71.4	21.4	7.1	3.7	
Sucrose	66.7	71.4	21.4	7.1	3.7	
Sucrose	60.0	71.4	21.4	7.1	3.7	
Sucrose	50.0	71.4	21.4	7.1	3.7	
PVP C-15	77.8	71.4	21.4	7.1	3.7	
PVP C-15	75.0	71.4	21.4	7.1	3.7	
PVP C-15	66.7	71.4	21.4	7.1	3.7	
PVP C-15	63.6	71.4	21.4	7.1	3.7	
Sucrose w/ Maltodextrin[2]	77.8	71.4	21.4	7.1	3.7	
Sucrose	77.8	63.6	30.0	6.4	3.7	

[1] Non-Essential Contents are in Aqueous Phase of the Primary Emulsion unless otherwise noted.

[2] 3% Maltodextrin in Sucrose.

I Claim:

1. A self-emulsifying glass comprising a mixture of an oleaginous material and a non-surface active, water soluble matrix compound, said glass being about 10% to about 60% microcrystalline as determined by differential scanning calorimetry, said glass being capable of forming a stable emulsion upon contact with a sufficient amount of an aqueous phase.

2. The glass of claim 1 wherein said matrix compound is selected from the group consisting of sucrose, trehalose, fructose, a cyclamate, a saccharine, and mixtures thereof.

3. The glass of claim 1 wherein said matrix compound is selected from the group consisting of a monosaccharide, a disaccharide, and a sweetener, wherein said matrix compound is at least about as sweet as sucrose.

4. The glass of claim 3 wherein said matrix compound is sucrose.

5. The glass of claim 4 wherein said mixture further comprises maltodextrin.

6. The glass of claim 1 further comprising a lipid soluble, active ingredient in said oleaginous material.

7. The glass of claim 6 wherein said lipid soluble active ingredient is a temperature sensitive active ingredient.

8. The glass of claim 1 wherein said oleaginous material is a water-in-oil emulsion.

9. The glass of claim 8 wherein the aqueous phase of said water-in-oil emulsion contains a water-soluble, active ingredient.

10. The glass of claim 1 wherein the weight ratio of said matrix compound to said oleaginous material is at least about 2:1.

11. The glass of claim 2 wherein the weight ratio of said matrix to said oleaginous material is between at least about 2:1 and about 20:1.

12. The glass of claim 1 in powdered form.

13. The glass of claim 1 in the form of a solid foam.

14. The glass of claim 1 wherein said oleaginous material is selected from the group consisting of a fluorodecalin, mineral oil, peanut oil, vegetable oil, corn oil, soybean oil, safflower oil and olive oil.

15. A self-emulsifying glass comprising a mixture of an oleaginous material and a non-surface active, water-soluble matrix compound which is selected from the group consisting of a polyvinylpyrrolidone, a cellulose derivative, a maltodextrin, a sweetener which is at least about as sweet as sucrose and mixtures thereof, said glass capable of forming a stable emulsion on contact with an aqueous phase.

16. The glass of claim 15 wherein said matrix compound is a polyvinylpyrrolidone.

17. The glass of claim 15 in powdered form.

18. The glass of claim 15 which is a solid foam.

19. The glass of claim 15 further comprising a lipid soluble active ingredient in said oleaginous material.

20. The glass of claim 19 wherein said lipid soluble active ingredient is temperature sensitive.

21. The glass of claim 15 wherein said oleaginous material comprises a water-in-oil emulsion.

22. The glass of claim 21 wherein the aqueous phase of said water-in-oil emulsion contains a water-soluble active ingredient.

23. The glass of claim 15 wherein the weight ratio of said matrix compound to said oleaginous material is at least about 2:1.

24. The glass of claim 15 wherein the oleaginous material is selected from the group consisting of fluorodecalin, mineral oil, peanut oil, vegetable oil, corn oil, soybean oil, safflower oil and olive oil.

25. A self-emulsifying glass comprising a mixture of an oleaginous material and a non-surface active, water-soluble matrix compound, the structure of which comprises a tripartite glucophore which contains an electronegative atom, a polarized bond and a hydrophobic region, said glass capable of forming a stable emulsion upon contact with a sufficient amount of an aqueous phase.

26. The glass of claim 25 being about 10% (w/w) to about 60% (w/w) microcrystalline.

27. The glass of claim 25 wherein said matrix compound is selected from the group consisting of sucrose, trehalose, fructose, a cyclamate, a saccharine, and mixtures thereof.

28. The glass of claim 25 wherein said matrix compound is selected from the group consisting of monosaccharides, disaccharides, and sweeteners which are at least about as sweet as sucrose.

29. The glass of claim 27 wherein said mixture further comprises maltodextrin.

30. The glass of claim 25 further comprising a lipid soluble, active ingredient in said oleaginous material.

31. The glass of claim 30 wherein said lipid soluble material is a temperature sensitive active ingredient.

32. The glass of claim 25 wherein said oleaginous material is a water-in-oil emulsion.

33. The glass of claim 32 wherein the aqueous phase of said water-in-oil emulsion contains a water-soluble, active material.

34. The glass of claim 25 wherein the weight ratio of said compound to said oleaginous material is at least about 2:1.

35. The glass of claim 25 in powdered form.

36. The glass of claim 25 in the form of a solid foam.

37. The glass of claim 25 wherein the oleaginous material is selected from the group consisting of mineral oil, peanut oil, vegetable oil, corn oil, soybean oil, safflower oil, and olive oil.

38. A self-emulsifying glass comprising a mixture of an oleaginous material and a non-surface active, water-soluble matrix compound selected from the group of monosaccharides, disaccharides and sweeteners wherein said compound is at least about as sweet as sucrose and wherein said oleaginous material contains a lipid soluble active ingredient which is temperature sensitive, said glass capable of forming an emulsion on contact with a sufficient amount of an aqueous phase.

39. The glass of claim 38 wherein said temperature sensitive active ingredient is a pharmaceutical agent.

40. The glass of claim 38 being about 10% to about 60% microcrystalline.

41. The glass of claim 38 wherein said temperature sensitive active ingredient decomposed of a temperature above about 140°C.

42. A self-emulsifying glass comprising a mixture of an oleaginous material and a non-surface active, water-soluble matrix compound selected from the group of polymers consisting of a polyvinylpyrrolidone, a cellulose derivative and a maltodextrin wherein said oleaginous material contains a lipid soluble material which is a temperature sensitive active material, said glass capable of forming an emulsion on contact with a sufficient amount of an aqueous phase.

43. A self-emulsifying glass comprising a mixture of a water-in-oil emulsion and a non-surface active, water-soluble matrix compound, the structure of which comprises a tripartite glucophore which contains an electronegative atom, a polarized bond and a hydrophobic region, said glass capable of forming a stable W/O/W emulsion on contact with a sufficient amount of an aqueous phase.

44. The glass of claim 43 wherein said matrix compound is selected from the group consisting of sucrose, fructose, trehalose, a cyclamate and a saccharine.

45. The glass of claim 43 wherein said matrix compound is selected from the group of a monosaccharide, a disaccharide and a sweetener, wherein each is at least about as sweet as sucrose.

46. The glass of claim 43 further comprising maltodextrin.

47. The glass of claim 43 wherein the aqueous phase of said water-in-oil emulsion contains an active ingredient.

48. A self-emulsifying glass comprising a mixture of a water-in-oil emulsion and a non-surface active, water-soluble polymer selected from the group consisting of a polyvinylpyrrolidone, a cellulose derivative and a maltodextrin, said glass capable of forming a stable W/O/W emulsion on contact with a sufficient amount of an aqueous phase.

49. The glass of claim 48 in which the aqueous phase of said water-in-oil emulsion contains an active ingredient.

50. A method for producing a self-emulsifying glass which is capable of forming a stable oil-in-water emulsion on contact with a sufficient amount of an aqueous phase comprising the steps of:

(a) combining an oleaginous material and a non-surface active, water-soluble matrix compound the structure of which comprises a tripartite glucophore which contains an electronegative atom, a polarized bond and a hydrophobic region and a quantity of a solvent sufficient to dissolve substantially all of said matrix compound to form a combination wherein said combination is not a stable emulsion;

(b) removing said solvent from said combination such that a glass results.

51. The method of claim 50 wherein said non-surface active, water-soluble matrix compound is selected from the group consisting of sucrose, trehalose, fructose, a cyclamate and a saccharine.

52. The method of claim 50 wherein said non-surface active, water-soluble matrix compound is selected from the group consisting of a monosaccharide, a disaccharide and a sweetener, wherein each is at least about as sweet as sucrose.

53. The method of claim 50 wherein said solvent is aqueous.

54. The method of claim 50 wherein said solvent is removed from said combination at a rate that is faster than the rate of crystallization of the non-surface active, water-soluble matrix compound.

55. The method of claim 50 in which said solvent is removed employing rotoevaporation.

56. The method of claim 50 in which the weight ratio of said non-surface active, water-soluble matrix compound to said oleaginous material is at least about 2:1.

57. The method of claim 50 in which a lipid soluble active ingredient is added to said oleaginous material.

58. The method of claim 57 in which said lipid soluble active ingredient is temperature sensitive.

59. The method of claim 50 in which said solvent removal step is performed at a temperature less than about 50°C.

60. The method of claim 50 which is performed at temperatures below the melting point of said non-surface active, water-soluble matrix compound.

61. A self-emulsifying glass produced by the method of claim 50.

62. A method for preparing a stable oil-in-water emulsion comprising the step of contacting the self-emulsifying glass produced by the method of claim 50 with a sufficient amount of an aqueous phase.

63. The method of claim 50 wherein said oleaginous material contains an aqueous phase and an emulsifying agent.

64. A method for producing a self-emulsifying glass capable of forming a stable emulsion on contact with

a sufficient amount of an aqueous phase comprising the steps of:

(a) combining an oleaginous material and a non-surface active, water-soluble polymer selected from the group consisting of a polyvinylpyrrolidone, a cellulose derivative and a maltodextrin and a quantity of a solvent sufficient to dissolve substantially all of said polymer to form a combination wherein said combination is not a stable emulsion; and

(b) removing said solvent from said combination such that said self-emulsifying glass results.

65. The method of claim 64 wherein said solvent is aqueous.

66. The method of claim 64 in which said solvent is removed employing rotoevaporation.

67. The method of claim 64 wherein said non-surface active, water-soluble polymer is polyvinylpyrrolidone and said solvent is chloroform.

68. The method of claim 64 in which the weight ratio of said non-surface active, water-soluble polymer to said oleaginous material is at least about 2:1.

69. The method of claim 64 in which a lipid soluble active ingredient is added to said oleaginous material.

70. The method of claim 64 in which said solvent removal step is performed at a temperature less than about 50°C.

71. The method of claim 64 which is performed at temperatures below the melting point of said non-surface active, water-soluble polymer.

72. The method of claim 64 wherein the oleaginous material contains an aqueous phase and an emulsifying agent.

73. A self-emulsifying glass produced by the method of claim 64.

74. A method for preparing a stable oil-in-water emulsion comprising the step of contacting the self-emulsifying glass produced by the method of claim 64 with a sufficient amount of an aqueous phase.

75. An emulsion produced by the method of claim 74.

76. A method for producing a self-emulsifying glass capable of forming a stable water-in-oil-in-water emulsion on contact with a sufficient amount of an aqueous phase, comprising the steps of:

(a) combining a water-in-oil emulsion with a non-surface active, water-soluble matrix compound, the structure of which comprises a tripartite glucophore which contains an electronegative atom, a polarized bone and a hydrophobic region and a quantity of a solvent sufficient to dissolve substantially all of said compound, wherein said combining step produced a combination; and

(b) removing said solvent from said combination leaving a glass.

77. The method of claim 76 wherein said non-surface active, water-soluble matrix compound is selected

from the group consisting of sucrose, trehalose, fructose, a cyclamate and a saccharine.

78. The method of claim 76 wherein said non-surface active, water-soluble matrix compound is selected from the group consisting of a monosaccharide, a disaccharide and a sweetener wherein each is at least about as sweet as sucrose.

79. The method of claim 76 wherein said solvent is water.

80. The method of claim 76 in which a lipid soluble active ingredient is added to said water-in-oil emulsion.

81. The method of claim 76 in which a water-soluble active ingredient is added to said water-in-oil emulsion.

82. The method of claim 76 in which said solvent removal step is performed at a temperature less than about 50°C.

83. The method of claim 76 performed at temperatures below the melting point of said non-surface active, water-soluble matrix compound.

84. The method of claim 76 wherein said solvent is removed by rotoevaporation.

85. A self-emulsifying glass produced by the method of claim 76.

86. A water-in-oil-in-water emulsion produced by the method of claim 76.

87. A method for producing a self-emulsifying glass capable of forming a stable water-in-oil-in-water emulsion on contact with a sufficient amount of an aqueous phase, comprising the steps of:

(a) combining a water-in-oil emulsion with a non-surface active, water-soluble polymer selected from the group consisting of a polyvinylpyrrolidone, a cellulose derivative and a maltodextrin, and a quantity of a solvent sufficient to dissolve substantially all of said polymer, wherein said combining step produces a combination; and

(b) removing said solvent from said combination leaving a glass.

88. The method of claim 87 in which said solvent is removed employing rotoevaporation.

89. The method of claim 87 in which the weight ratio of said non-surface active, water-soluble polymer to said oleaginous material is at least about 2:1.

90. The method of claim 87 in which a lipid soluble active ingredient is added to said water-in-oil emulsion material.

91. The method of claim 87 in which a water-soluble active ingredient is added to said water-in-oil emulsion aqueous phase of step (a).

92. The method of claim 87 in which said solvent removal step is performed at a temperature less than about 50°C.

93. The method of claim 87 performed at temperatures below the melting point of said non-surface active, water-soluble polymer.

94. A self-emulsifying glass produced by the method of claim 87.

95. A water-in-oil-in-water emulsion produced by the method of claim 87.

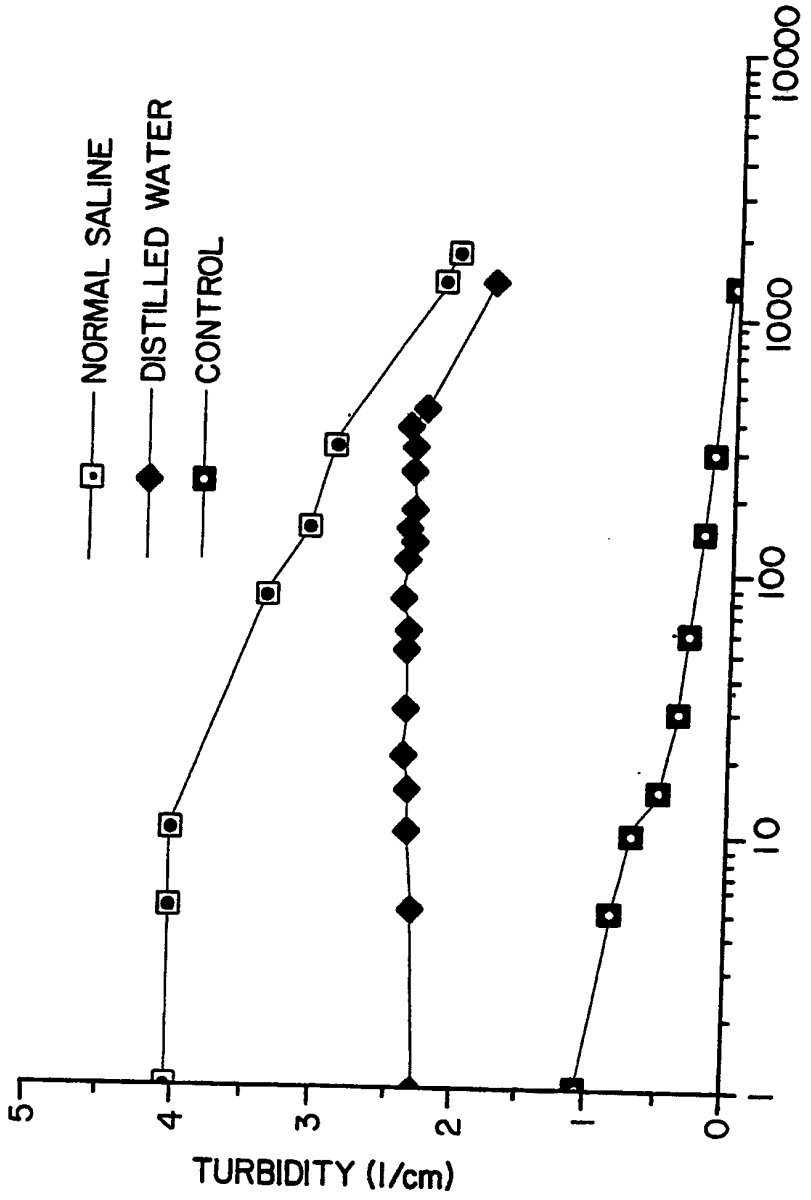

NORMAL SALINE
DISTILLED WATER
CONTROL
TURBIDITY (1/cm)
5
4
3
2
1
0
MINUTES
10000
1000
100
10
1

FIG. 1

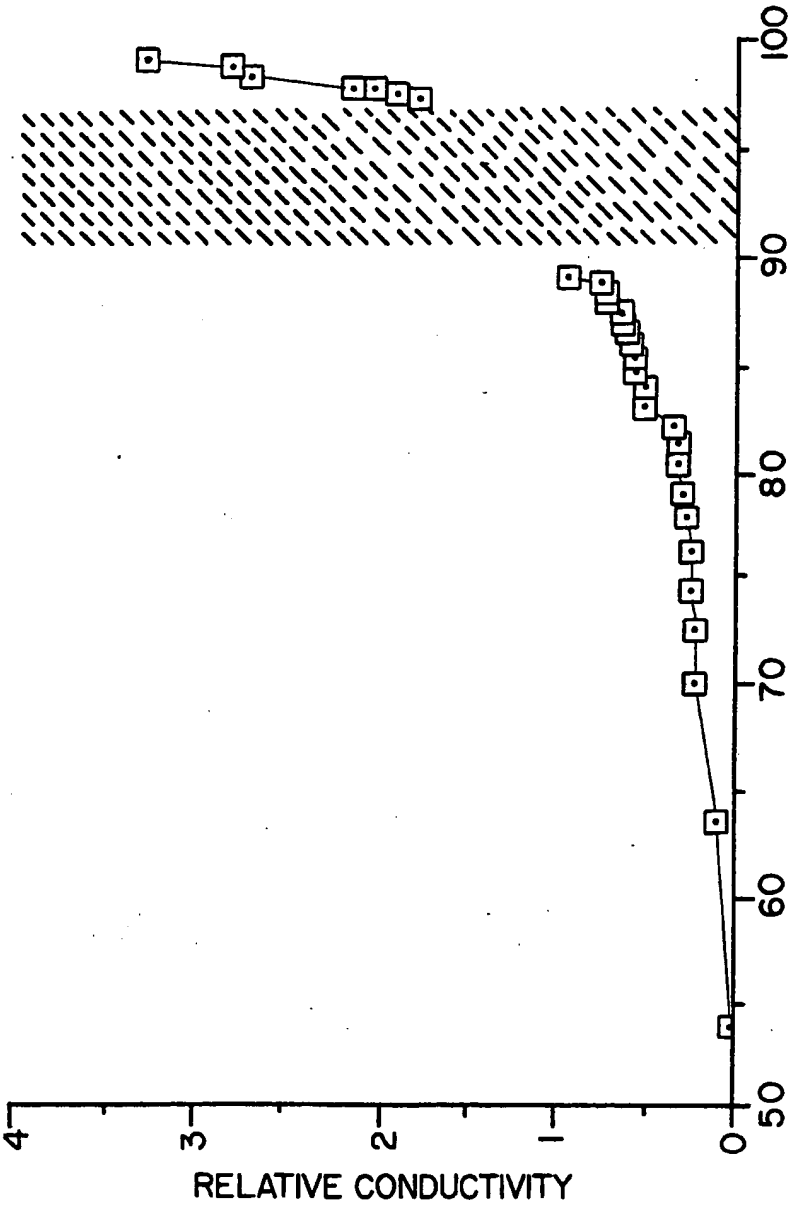


FIG. 2

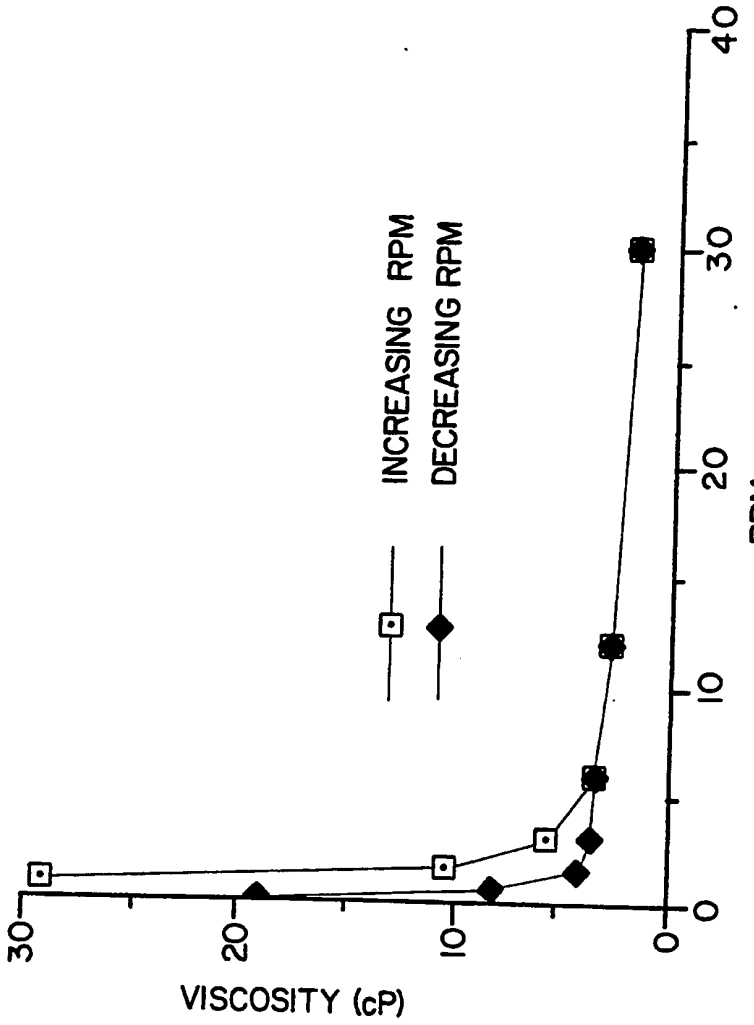

INCREASING RPM
DECREASING RPM
RPM
0
10
20
30
40
VISCOSITY (cP)
30
20
10
0

FIG. 3

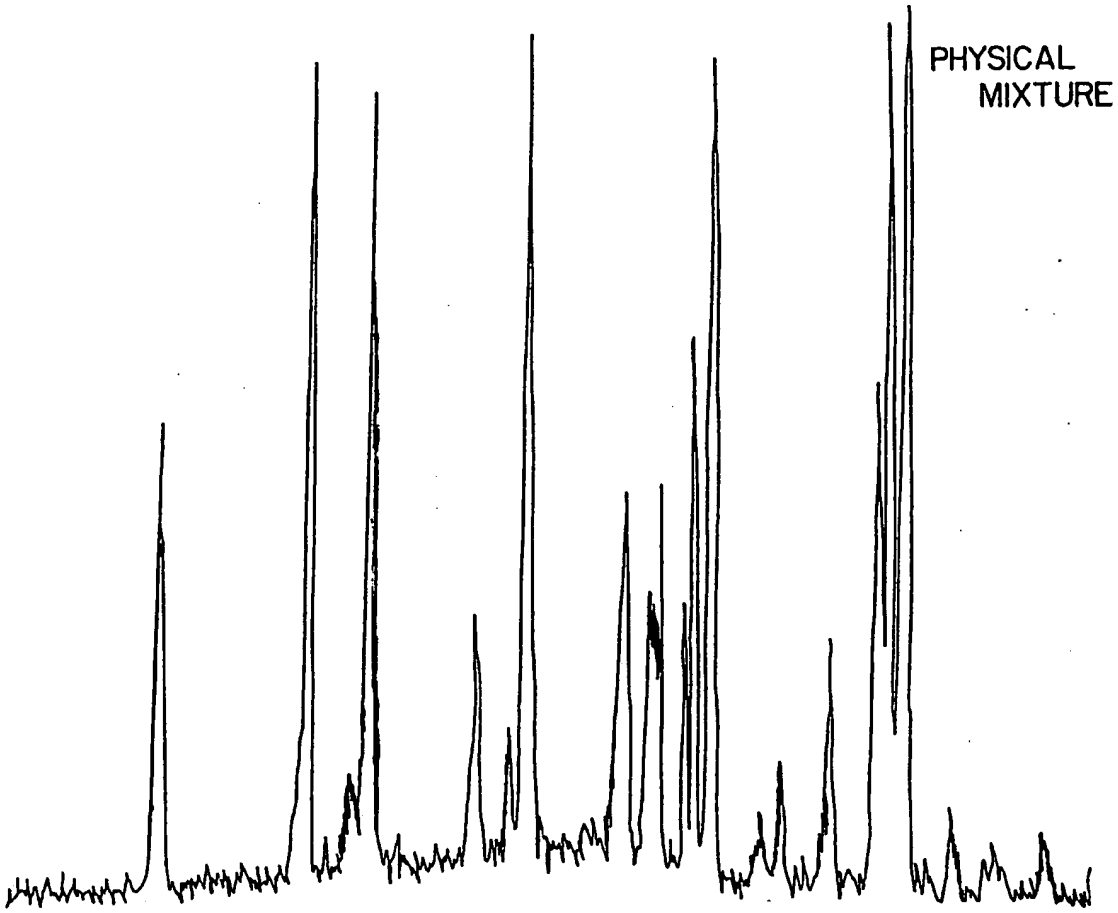
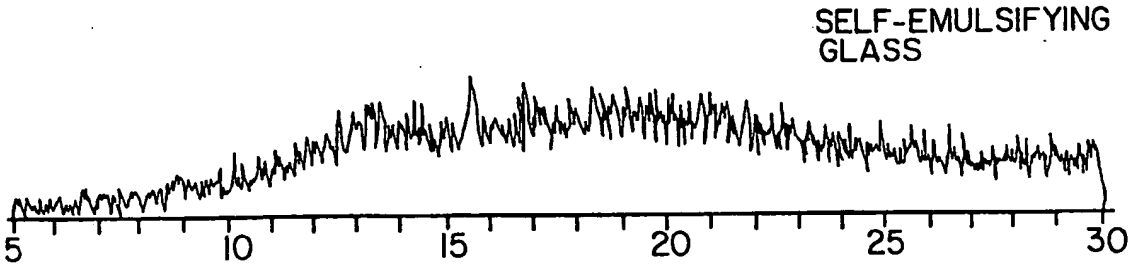


FIG. 4A



SUCROSE: MINERAL OIL = 3.5:1

FIG. 4B

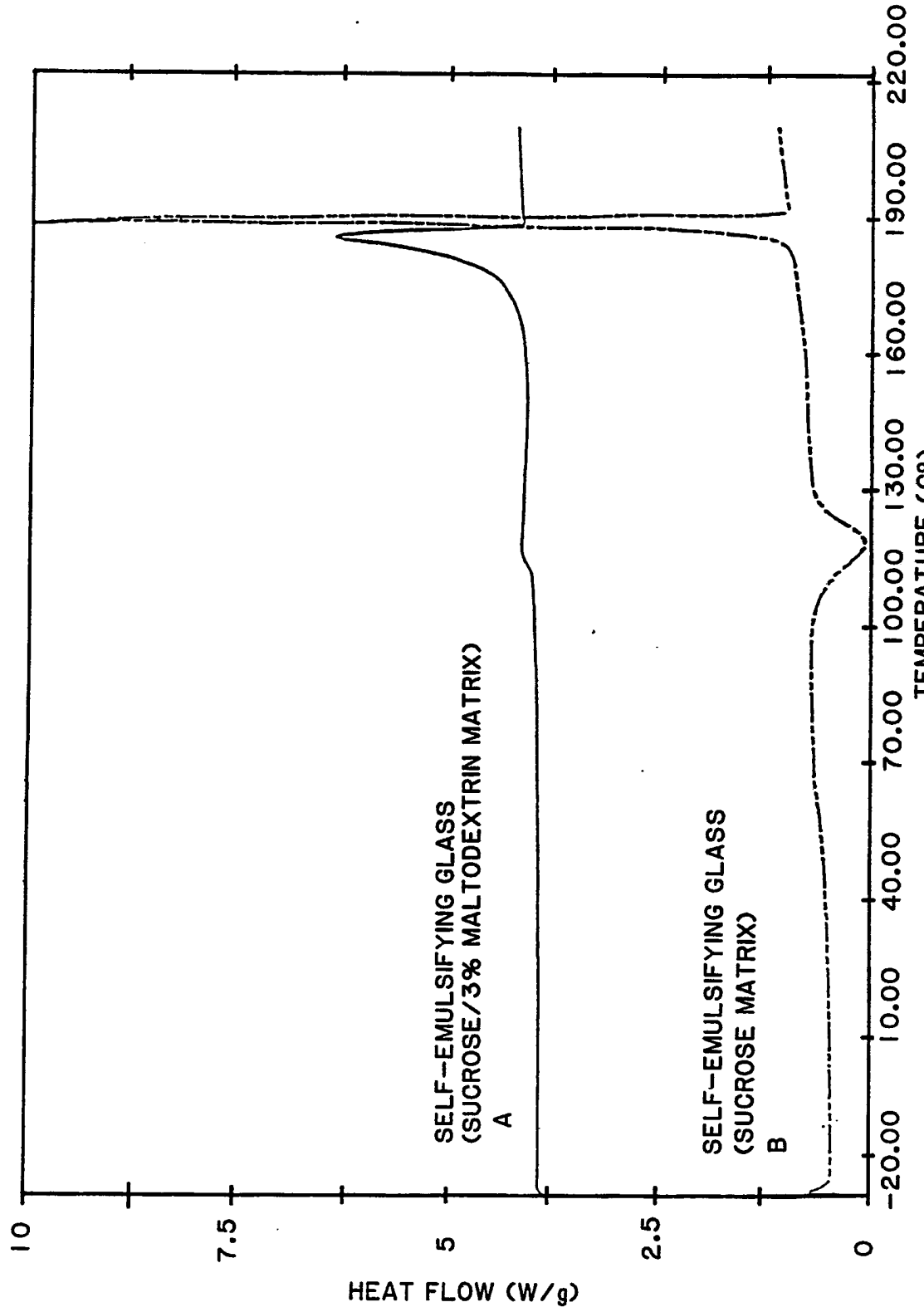

SELF-EMULSIFYING GLASS
(SUCROSE/3% MALTODEXTRIN MATRIX)
A
SELF-EMULSIFYING GLASS
(SUCROSE MATRIX)
B
HEAT FLOW (W/g)
10
7.5
5
2.5
0
-20.00
10.00
40.00
70.00
100.00
130.00
160.00
190.00
220.00
TEMPERATURE (C°)

FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/03864

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 31/74
U.S. CL. 424/78, 81; 426/602

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/78, 81; 426/602

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US, A,2,861,920 (DALE) 25 NOVEMBER 1958. See working examples.	1-95
Y	US, A, 3,136,692 (BANDELIN) 09 JUNE 1964. See working examples.	1-95
Y	US, A, 4,199,564 (SILVER) 22 APRIL 1980. See columns 6-8.	1-95
P,Y	US, A, 4,963,385 (ANTRIM) 16 OCTOBER 1990. See columns 4-6.	1-95
Y	US, A, 3,148,127 (MARSH) 08 SEPTEMBER 1964. See columns 2-3.	1-95
Y	US, A, 3,145,146 (LIEBERMAN) 18 AUGUST 1964. See working examples.	1-95
Y	"The Theory and Practice of Industrial Pharmacy". (LACHMAN), (1976) pages 519-524. See entire document.	1-95

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
24 July 1991	24 SEP 1991
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Peter Kulkosky

Form PCT/ISA/210 (second sheet) (May 1988)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
P,Y	WO, A, 90/06969 (FUISZ PHARMACEUTICAL LTD) 28 JUNE 1990. See working examples.	1-95